(6)

Supreme Court, U.S.
FILED
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No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

JOINT APPENDIX

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PETITION FOR CERTIORARI FILED MARCH 2, 2004
CERTIORARI GRANTED JANUARY 7, 2005

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APPENDIX 1 — RELEVANT DOCKET ENTRIES OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Court: U.S. COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Case Title: INTEGRA LIFESCIENCES v. MERCK

Appeal From: SOUTHERN DISTRICT OF CALIFORNIA

Filed On: 11/09/2001

CASE INFORMATION

Case Number: **02-1052**

LOWER COURT INFORMATION

Docket Number: 96-CV-1307
Date NOA Filed: 11/07/2001

DOCKET PROCEEDINGS

ENTRY #:	DATE:	DOCKET ENTRY:
	12/10/2003	MANDATED ON
25	7/2/2003	ERRATA SHEET SENT TO PARTIES. SERVICE : BY MAIL ON 7/2/2003

24	6/16/2003	ACTION GRANTED. THE PETITION IS DUE 7/21/03.
23	6/13/2003	MOTION BY APPELLANT - MOTION FOR A THIRTY-DAY ENLARGEMENT OF TIME TO FILE A PETITION FOR PANEL REHEARING AND/OR FOR REHEARING EN BANC. SERVICE : BY MAIL ON 6/12/2003
	6/6/2003	DISPOSITION: AFFIRMED-IN-PART, REVERSED-IN-PART, AND REMANDED; BY PANEL
22	2/10/2003	APPELLANT'S RESPONSE TO APPELLEE'S CITATION OF SUPPLEMENTAL AUTHORITY PURSUANT TO RULE 28(H). (SENT TO PANEL) SERVICE : BY MAIL ON 2/10/2003
21	2/7/2003	CROSS APPELLANT'S CITATION OF SUPPLEMENTAL AUTHORITY PURSUANT TO RULE 28(H). (SENT TO PANEL) SERVICE : BY HAND ON 2/7/2003

	11/5/2002	ORAL ARGUMENT DATE / CALENDARED
	7/19/2002	CROSS APPELLANT REPLY BRIEF FILING DATE
15	6/18/2002	APPELLANT REPLY BRIEF FILING DATE
13	4/25/2002	APPELLEE OR CROSS APPELLANT PRINCIPAL BRIEF FILING DATE
	2/13/2002	APPELLANT PRINCIPAL BRIEF FILING DATE
6	12/17/2001	ORDERED: MOTION DENIED. (SEE DKT #1). IF SCRIPPS AND CHERESH INTEND TO PARTICIPATE IN THIS APPEAL, COUNSEL SHOULD ENTER APPEARANCES ON THEIR BEHALF AND THEY WILL BE DESIGNATED AS DEFENDANTS-APPELLES IN THE CAPTION. BY: MOTION PANEL. JUDGE: NEWMAN.

Court: U.S. COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Case Title: INTEGRA LIFESCIENCES v. MERCK

Appeal From: SOUTHERN DISTRICT OF CALIFORNIA

Filed On: 11/27/2001

CASE INFORMATION

Case Number: **02-1065**

LOWER COURT INFORMATION

Docket Number: 96-CV-1307

OTHER CASES

Relationship: **Lead Docket:**

LEAD CASE **02-1052**

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DOCKET PROCEEDINGS

ENTRY #:	DATE:	DOCKET ENTRY:
	12/10/2003	MANDATED ON 6/6/2003 DISPOSITION: AFFIRMED-IN-PART, REVERSED-IN-PART, AND REMANDED; BY PANEL

APPENDIX 2 — RELEVANT DOCKET ENTRIES OF THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF CALIFORNIA (SAN DIEGO)

CIVIL DOCKET FOR CASE #: 96-CV-1307

Integra Lifesciences, et al v. Merck KGaA, et al

Filed: 07/18/96
Assigned to: Judge Rudi M. Brewster
Referred to: Magistrate Judge Anthony J. Battaglia
Demand: $0,000
Nature of Suit: 830
Lead Docket: None
Jurisdiction: Federal Question
Dkt# in other court: None
Cause: 35:271 Patent Infringement

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(See Above)
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(See above)
[COR LD NTC]

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[term 03/27/01]
(See above)
[COR LD NTC]

DOES, 1 - 25 inclusive
defendant

==========

7/18/96	1	Complaint Filed; Summons(es) issued to 7/18/96 (referred to Magistrate Anthony J. Battaglia) Receipt No/Amt of #24024/$120 (acr) [Entry date 07/22/96]
8/26/96	5	Answer to complaint and Counterclaim by defendant Scripps Research, defendant David A Cheresh t/w prf svc (acr) [Entry date 09/19/96]
9/18/96	7	Answer to counterclaims by counter-defendant Telios Pharmaceutica, counter-defendant Burnham Institute to Counterclaim; demand for jury trial t/w prf svc (acr) [Entry date 09/19/96]

10/24/96	22	Answer by defendant Merck KGaA, defendant Scripps Research, defendant David A Cheresh t/w prf svc (tb) [Entry date 10/29/96]
11/12/96	28	Answer by counter-defendant Telios Pharmaceutica, counter-defendant Burnham Institute to Counterclaim, demand for jury trial t/w prf svc (tb) [Entry date 11/18/96]
5/16/97	74	Notice of motion and Motion by defendant Merck KGaA, defendant Scripps Research, defendant David A Cheresh for partial summary judgment [motion(s) referred to Judge Judith N. Keep] motion hrg set for 8/4/97 at 10:30 (tb) [Entry date 05/22/97]
5/16/97	75	Document Sealed (pursuant to Court Order) Memo of p/a's re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	76	Document Sealed (pursuant to Court Order) Declaration of Dr Cheresh re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	77	Document Sealed (pursuant to Court Order) Declaration re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]

5/16/97	78	Document Sealed (pursuant to Court Order) Declaration re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	79	Document Sealed (pursuant to Court Order) Declaration re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	80	Document Sealed (pursuant to Court Order) Declaration re motion for partial summary judgment [74-1] (tb) [Entry date 05/22/97]
5/16/97	81	Notice of motion and Motion by defendant Merck KGaA, defendant Scripps Research, defendant David A Cheresh for protective order limiting discovery [motion(s) referred to Judge Judith N. Keep], motion hrg set for 8/4/97 at 10:30 t/w prf svc (tb) [Entry date 05/22/97]
5/20/97	85	Statement material of facts by defendant Merck KGaA, defendant Scripps Research, defendant David A Cheresh in support of motion for partial summary judgment [74-1] (tb) [Entry date 05/23/97]
8/2/99	579	Motions in limine no. 14 of 23 by plaintiff Integra Lifescience, plaintiff Burnham Institute re European Clinical trials, and untimely produced or previously withheld documents and testimony, [motion(s) referred to Judge Thomas J. Whelan]

		motion hrg set for 9/20/99 at 10:30; t/w exhibits. (lmh) [Entry date 08/05/99]
8/2/99	581	Motions in limine no. 16 of 23 by plaintiff Integra Lifescience, plaintiff Burnham Institute to exclude the portions of Dr. Bynum's expert witness testimony that are based on legal conclusions, [motion(s) referred to Judge Thomas J. Whelan], motion hrg set for 9/20/99 at 10:30; t/w exhibits. (lmh) [Entry date 08/05/99]
8/5/99	595	Notice of Motion and Motion in limine no. ! by defendants (to exclude expert testimony of Gerald Meyer), [motion(s) referred to Judge Thomas J. Whelan], motion hrg set for 9/13/99 at 10:00. (lmh) [Entry date 08/09/99]
8/5/99	596	Memorandum of Points and Authorities by defendants in support of motion in limine no. 1 (to exclude expert testimony of Gerald Meyer) [595-1]; t/w exhibits. (lmh) [Entry date 08/09/99]
8/5/99	597	Declaration of Matthew F. Weil by defendants in support of motion in limine no. 1 (to exclude expert testimony of Gerald Meyer) [595-1]; t/w exhibits. (lmh) [Entry date 08/09/99]

8/5/99 598 Notice of Motion and Motion in limine no. 2 by defendants (to exclude testimony or argument concerning the meaning of the word "solely" in 35 USC 271(E)(1)), [motion(s) referred to Judge Thomas J. Whelan], motion hrg set for 9/13/99 10:00. (lmh) [Entry date 08/09/99]

8/23/99 649 Memo of P/A in Opposition by defendants to plas' motion in limine no. 16 (re excluding the portions of Dr. Bynum's expert witness testimony that are based on legal

8/25/99 669 Opposition by plaintiffs to motion in limine no. 1 (to exclude expert testimony of Gerald Meyer) [595-1]; t/w exhibits. (lmh) [Entry date 08/25/99]

8/25/99 670 Opposition by plaintiffs to dfts' motion in limine no. 2 (to exclude testimony or argument concerning the meaning of the word "solely" in 35 USC 271(E)(1)) [598-1]; t/w exhibit. (lmh) [Entry date 08/25/99]

9/10/99 692 Reply by plaintiffs in support of motion in limine no. 10 to exclude Armitage testimony in its entirety - no testimony or evidence re legal analysis, legislative history, or applying the facts to the law [575-1] (lmh) [Entry date 09/13/99]

9/10/99 700 Reply by plaintiffs in support of motion in limine no. 16 to exclude the portions of Dr. Bynum's expert witness testimony that are based on legal conclusions [581-1] (lmh) [Entry date 09/13/99]

9/10/99 712 Reply by defendants in support of motion in limine no. 1 (to exclude expert testimony of Gerald Meyer) [595-1] (lmh) [Entry date 09/14/99]

10/4/99 743 Document Sealed (pursuant to Court Order): Dfts' Memo of P/A in Opposition re motion to exclude the IXSYS IND document production [730-1], re motion for evidentiary sanction of exclusion of said document [730-2] (lmh) [Entry date 10/05/99]

10/15/99 785 Order by Judge Thomas J. Whelan: Granting dfts' motion in limine no. 2 (to exclude testimony or argument concerning the meaning of the word "solely" in 35 USC 271(E)(1)) [598-1]. (lmh) [Entry date 10/18/99]

1/5/00 844 Order by Judge Thomas J. Whelan granting in part/denying in part motion in limine no. 14 re European Clinical trials [579-1], granting in part/denying in part motion in limine no. 14 untimely produced or previously withheld documents and testimony [579-2] (llh) [Entry date 01/05/00]

1/25/00 874 Designation of Interrogatory Responses, Responses to Request for Admissions and Responses to Document Requests by plaintiff Intergra Lifescience, plaintiff Burnham Institute (jah) [Entry date 01/27/00]

1/25/00 876 Proposed Jury Instructions submitted by plaintiff Intergra Lifescience, plaintiff Burnham Institute (jah) [Entry date 01/27/00]

1/25/00 877 Proposed Verdict Form by plaintiff Intergra Lifescience, plaintiff Burnham Institute (jah) [Entry date 01/27/00]

1/25/00 880 Designation of Plaintiffs' Responses to Interrogatories by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA (jah) [Entry date 01/27/00]

1/26/00 870 Supplemental Designation by plaintiff Intergra Lifescience, plaintiff Burnham Institute of Interrogatory Responses, Responses to Request for Admissions and Responses to Document Requests (jah) [Entry date 01/26/00]

2/2/00 918 Minutes: Enter Order by Judge Thomas J. Whelan granting in part/denying in part request to modify pretrial conference order

[891-1];Dft's request to designate tissue expert - denied; Dft's request to add an exhibit to trial exhibit list, (investigational new drug application) - denied; Dft's request to add exhibit to trial exhibit list - (article of Brower) - denied; Dft's request to add exhibit to trial exhibit list (articles of Brassard, Kang, Wolosker) - denied; Dft's request to add 102(b) defense - denied; Dft's request to read deposition testimony of expert, Armitage - granted; Court Reporter: Linda Nelson (jah) [Entry date 02/04/00]

2/9/00 929 Second Amended Proposed Joint and Disputed Preliminary Jury Instructions (2nd set) (Rec'd in Docketing 2/14/00) (jah) [Entry date 02/14/00]

2/11/00 942 Order re defendants' one-page submission by Judge Thomas J. Whelan; issue one, denied amended order to follow; issue two, cross-examination is permissable on any "doors" agreed by plaintiff; issue three, IXSYS IND is admissable, NCI and IND is not (bar) [Entry date 02/16/00]

2/17/00 947 Memorandum of Points and Authorities in Opposition by defendants and counterclaimants David A Cheresh, Scripps Research, Merck KGaA to plaintiff's renewed motion to exclude expert testimony (No Motion filed, response to request) (jah) [Entry date 02/18/00]

2/24/00 950 Order by Judge Thomas J. Whelan re: use of NCI-IND at trial. (vls) [Entry date 02/24/00] [Edit date 02/28/00]

2/24/00 952 Submission re plas' introduction of evidence re excluded NCI Inc by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA of filing (sld) [Entry date 02/29/00]

3/7/00 970 Opposition by plaintiff Intergra Lifescience, plaintiff Burnham Institute to motion to dismiss claims against defendants The Scripps Research Institute and Dr. David A. Cheresh [957-1] (sld) [Entry date 03/08/00]

3/7/00 971 Opposition by plaintiff Intergra Lifescience, plaintiff Burnham Institute to motion for judgment as a matter of law at the closeof plaintiffs' case in chief [960-1]; t/w exhibit (sld) [Entry date 03/08/00]

3/8/00 975 Opposition by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA to plas' effort to exclude the testimony of L.L. Houston; t/w exhibits (sld) [Entry date 03/09/00]

3/13/00 978 Notice of Motion and Motion by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA for judgment as a matter of law at the close of evidence; [motion(s) referred to Judge

James M. Fitzgerald] (sld) [Entry date 03/13/00]

3/13/00 979 Opposition by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA to motion for judgment as a matter of law at the close of plaintiffs' case in chief [960-1] (sld) [Entry date 03/13/00]

3/13/00 980 Reply by defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA to opposition to motion for judgment as a matter of law at the closeof plaintiffs' case in chief [960-1] (sld) [Entry date 03/13/00]

3/13/00 981 Reply by defendant David A Cheresh, defendant ScrippsResearch, defendant Merck KGaA to opposition to renewed motion to dismiss claims against defendants The Scripps Research Institute and Dr. David A. Cheresh [957-1] (sld) [Entry date 03/13/00]

3/15/00 990 Objections by defendant Merck KGaA to jury [989-1]; t/w exhibits (sld) [Entry date 03/20/00]

3/16/00 991 Proposed jury instructions submitted by defendant Merck KGaA; t/w exhibits (sld) [Entry date 03/20/00]

3/16/00 992 Exceptions and objections by defendant Merck KGaA to jury charge and verdict form; t/w exhibit (sld) [Entry date 03/20/00]

3/16/00 993 Jury instructions submitted (rec'd 3/21/00) (sld) [Entry date 03/21/00] [Edit date 03/21/00]

3/17/00 994 Minutes: Enter Order by Judge James M. Fitzgerald: jury sequestered for lunch. Jury returns from deliberations at 1:50 pm; verdict in favor of pla and agaisnt dfts. Damages awarded in amount of $15 million. Affirmed by polling; jgm to be prepared by ct. Any pending pretrial motions are deemed to be moot; trial ended; t/w witness and exhibit list. Court Reporter: Linda Nelson (sld) [Entry date 03/21/00]

3/17/00 995 Jury verdict for plaintiff Intergra Lifescience, plaintiff Burnham Institute against defendant David A Cheresh, defendant Scripps Research, defendant Merck KGaA in the amount of $15 million (sld) [Entry date 03/21/00]

3/20/00 996 Minutes: Enter Order by Judge James M. Fitzgerald: the ct orders a stay of the entry of jgm, following a jury verdict, in this case until further order of the ct. Court Reporter: n/a (sld) [Entry date 03/21/00]

9/29/00 1033 Judgment: by Judge James M. Fitzgerald; judgment in favor of plaintiffs and against defendant Merck KGaA; plaintiffs are entitled to recover against Merck KGaA $15,000,000 in damages to compensate plaintiffs for Merck's infringement and inducing infringement; plaintiffs are entitled to recover against Merck KGaA prejudment interest in the amount of $1,125,000 and post judgment interest from the date of entry of this judgment until paid; terminating party Merck KGaA and terminating the case (bar) [Entry date 09/29/00] [Edit date 10/02/00]

10/11/00 1036 Amended Judgment: by Judge James M. Fitzgerald; judgment is amended to correct a typographical error in paragraph 6. (corrected "...post judgment interest from the date of entry of this judgment until paid.") (llh) [Entry date 10/12/00]

10/16/00 1047 Notice of Motion and Motion (No.1 of 6) by defendant and counter-claimant Merck KGaA for judgment as a matter of law on the FDA exemption 35:271(e)(1) [motion(s) referred to Judge James M. Fitzgerald] motion hrg set for 11/13/00 at 10:30 (llh) [Entry date 10/17/00]

10/16/00 1048 Memorandum of points and authorities by dft and counter-claimant Merck KGaA

in support of motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (llh) [Entry date 10/17/00]

10/16/00 1049 Declaration of Matthew F. Weil by dft and counter-claimant Merck KGaA re motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (llh) [Entry date 10/17/00]

10/16/00 1050 Notice of Motion and Motion (2 of 6) by dft and counter-claimant Merck KGaA for new trial re section 271(e)(1) defense [motions referred to Judge James M. Fitzgerald] motion hrg set for 11/13/00 at 10:30 (llh) [Entry date 10/17/00]

10/16/00 1051 Memorandum of points and authorities by dft and counter-claimant Merck KGaA in support of motion for new trial re section 271(e)(1) defense [1050-1] (llh) [Entry date 10/17/00]

10/16/00 1052 Declaration of M. Patricia Thayer by dft and counter-claimant Merck KGaA re motion for new trial re section 271(e)(1) defense [1050-1] (llh) [Entry date 10/17/00]

11/15/00 1078 Amended Stipulation and Order by Judge James M. Fitzgerald to stay execution of jgm pursuant to FRCP 62(b) and to

modify schedule for briefing post-judgment motions; ct stays execution of any and all proceedings to enforce the jgm in this matter until all of the pending mots for new trial or to alter or amd the jgm pursuant to Rule 59, jgm as a matter of law pursuant to Rule 50, and the pending mot to alter or amd the jgm pursuant to Rule 59 and Merck's period to appeal from the final jgm in this case has run; ct revised briefing schedule on six pending post-jgm mots of Merck; opp ddl reset to 11/20/00 as to all six pending mots, reply ddl reset to 12/8/00 as to all six pending motions; motion for new trial re damages [1062-1], motion for judgment as a matter of law re damages [1058-1] , re motion for new trial re patent invalidity and non-infringement [1055-1] re motion for judgment as a matter of law after jury verdict re patent invalidity and non-infringement [1053-1], re motion for new trial re section 271(e)(1) defense [1050-1] , re motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] , re motion to amend the judgment under FRCP 59(e) [1041-1]; ct will schedule a hrg is necessary. (llh) [Entry date 11/16/00]

11/20/00	1083	Opposition by plaintiff Intergra Lifescience, plaintiff Burnham Institute to motion (1 of 6) for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (llh) [Entry date 11/21/00]
11/20/00	1084	Declaration of David M. Beckwith by plaintiff Intergra Lifescience, plaintiff Burnham Institute re motion (1 of 6) for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (llh) [Entry date 11/21/00]
11/20/00	1085	Opposition by plaintiff Intergra Lifescience, plaintiff Burnham Institute to motion (2 of 6) for new trial re section 271(e)(1) defense [1050-1] (llh) [Entry date 11/21/00]
11/20/00	1086	Declaration of David M. Beckwith by plaintiff Intergra Lifescience, plaintiff Burnham Institute re motion (2 of 6) for new trial re section 271(e)(1) defense [1050-1] (llh) [Entry date 11/21/00] [1100-1] (tkl) [Entry date 12/05/00]
12/8/00	1103	Reply memorandum by counter-claimant Merck KGaA, defendant Merck KGaA, in support of motion for new trial re section 271(e)(1) defense [1050-1] (post-jgm motion 2 of 6) (tkl) [Entry date 12/11/00]

12/8/00	1106	Supplemental Declaration of Matthew F. Weil by counter-claimant Merck KGaA, defendant Merck KGaA in support of motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (post-jgm motion no.1 of 6) (tkl) [Entry date 12/11/00]
12/8/00	1107	Reply Brief Filed by counter-claimant Merck KGaA, defendant Merck KGaA in support of motion for judgment as a matter of law on the FDA exemption 35:271(e)(1) [1047-1] (tkl) [Entry date 12/11/00]
12/8/00	1110	Reply Declaration of M. Patricia Thayer by counter-claimant Merck KGaA, defendant Merck KGaA re motion for new trial re section 271(e)(1) defense [1050-1]; (post-jgm motion no 2 of 6) (tkl) [Entry date 12/11/00]
12/8/00	1112	Proof of service by counter-claimant Merck KGaA, defendant Merck KGaA by mail re replies in support of post jgm motions for new trial (tkl) [Entry date 12/11/00]
3/6/01	1133	Order by Judge James M. Fitzgerald denying Merck's motion for judgment as a matter of law [1047-1] (tkl) [Entry date 03/07/01]

3/21/01	1135	Order by Judge James M. Fitzgerald: Merck's mot for new trial on the 271(e) defense [1050-1] is denied (tkl) [Entry date 03/22/01]
3/27/01	1136	Second amended jgm and Order by Judge James M. Fitzgerald: plas to recover from Merck $15,000,000 in damages and pla's to recover against Merck KGaA prejgm interest through 4/30/01 of $1,125,000 w/ further prejgm interest accruing from 4/ 30/00; terminating dfts David Cheresh and Scripps Research Institute. (tkl) [Entry date 03/28/01]

APPENDIX 3 — EXCERPT FROM PLAINTIFFS' SUPPLEMENTAL AMENDED COMPLAINT FOR PATENT INFRINGEMENT, DOCKET # 520

[Commencing at page 1]

Plaintiffs, for their supplemental amended complaint, herein allege as follows:

1. Plaintiff Integra LifeSciences I, Ltd. ("'Integra") is a corporation organized under the laws of the state of Delaware and duly authorized to transact business in this state. Integra acquired, through merger, all of the intellectual property rights previously owned by Telios Pharmaceuticals, Inc., pursuant to merger in December 1996. Telios Pharmaceuticals, Inc. was the former licensee of all of the patents at issue in this litigation. Pursuant to the above-described merger, Integra is currently the licensee of all of the patents described in this lawsuit.

2. Plaintiff The Burnham Institute, formerly known as La Jolla Cancer Research Foundation, is a nonprofit corporation incorporated under the laws of the state of California with its principal place of business in this judicial district.

3. Upon information and belief, Defendant Merck KGaA ("Merck") is a corporation incorporated under the laws of Germany, and with its principal place of business in Darmstadt, Germany.

4. Upon information and belief, Defendant The Scripps Research Institute ("Scripps") is a nonprofit corporation incorporated under the laws in the state of California with its principal place of business in this judicial district.

5. Upon information and belief, Defendant David A. Cheresh is a natural person residing in the state of California within this judicial district and works as a researcher for Defendant Scripps.

JURISDICTION AND VENUE

6. This action arises under the patent laws of the United States of America and jurisdiction is founded on Title 28, United States Code, §§ 1331 and 1338(a).

7. Venue is proper in this Court under Title 28, United States Code, § 1400(b).

FIRST CLAIM FOR RELIEF FOR INFRINGEMENT OF THE '525 PATENT AGAINST ALL DEFENDANTS

8. On December 1988, United States Patent No. 4,792,525 (the " '525 Patent") a copy of which is attached hereto as Exhibit A was duly and legally issued to La Jolla Cancer Research Foundation, now known as The Burnham Institute, as sole assignee of all rights in said patent from inventors Erkki Ruoslahti, Ph.D. and Michael Pierschbacher, Ph.D. The Burnham institute, which is the sole owner of the '525 Patent, exclusively licensed all rights in said patent to Telios Pharmaceuticals, Inc., which was subsequently acquired through merger by Integra. Pursuant to said exclusive license Integra has the right to sue and to recover for infringement of the '525 Patent.

9. Upon information and belief, Defendant Merck with actual knowledge of the '525 Patent, has willfully and deliberately induced and continues to willfully and deliberately induce Defendants Scripps and Cheresh to infringe the '525 Patent.

APPENDIX 4 — ORDER DENYING DEFENDANTS' MOTION FOR PARTIAL SUMMARY JUDGMENT RE 35 U.S.C. § 271(e), DOCKET # 181

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

CASE NO. 96-CV-1307

TELIOS PHARMACEUTICALS, INC., and
THE BURNHAM INSTITUTE,

Plaintiffs,

vs.

MERCK KGaA, THE SCRIPPS RESEARCH INSTITUTE,
and DR. DAVID CHERESH,

Defendants.

ORDER DENYING DEFENDANTS' MOTION FOR PARTIAL SUMMARY JUDGMENT RE 35 U.S.C. § 271(e)

Defendants Merck KGaA, Scripps Research Institute and Dr. David A. Cheresh collectively move under F.R.C.P. Rule 56 for partial summary judgment. Plaintiffs Telios Pharmaceuticals, Inc., and the Burnham Institute oppose. Oral arguments were heard on Tuesday, September, 2, 1997. Based on the briefs and arguments submitted, the court denies defendants' motion for partial summary judgment.

I. Background

This patent infringement case arises out of a dispute concerning plaintiffs' '525 patent. The patent, entitled "Tetrapeptide", relates to peptides, which promote cell attachment and is described to include the amino acids: Arg—Gly—Asp—R.

Defendant Scripps is a non-profit corporation that conducts biochemical research. Defendant Dr. Cheresh is a member of the Immunology Department at Scripps. During the past decade, Dr. Cheresh has conducted ongoing research of certain proteins and peptides. Defendant Merck is a German pharmaceutical corporation which collaborates with Scripps' research projects including those involving Dr. Cheresh.

In late 1988, defendants Merck and Scripps entered into a research support agreement for Dr. Cheresh's lab. Under the terms of this agreement, Merck provided Dr. Cheresh with funding for his research. In return, Scripps granted Merck an option to license any future discoveries that might stem from Dr. Cheresh's laboratory. The parties concede that Dr. Cheresh's research has included discoveries that involve the Arg—Gly—Asp—R chain of amino acids allegedly covered by the '525 patent. Dr. Cheresh discovered that by binding a substance to special molecules on the surface of cells, he could stem the growth of new blood vessels, and potentially, the growth of tumors. This lawsuit centers upon that discovery and the defendants' effort to bring the discovery to market in the form of an FDA approved drug.

Beginning in 1989, Merck began to provide Dr. Cheresh with samples of new and unique peptides for his experiments.

Most of the peptides sent by Merck to Dr. Cheresh from 1989 to 1995 did not merit further study. However, two of the modified cyclopeptides, identified as EMD, 66203 and EMD 85189, exhibited adequate promise to potentially develop into a marketable drug. Of the two, EMD 85189 was found to be more effective at "starving" tumor tissue of the needed blood supply.

Based on these results, the defendants signed a new series of agreements. Most notably, in September, 1995, Merck and Scripps signed a "Research Funding and Option Agreement" allegedly detailing a program to develop a new drug for FDA approval based on Dr. Cheresh's research. Defendants contend that since September, 1995, all the Merck cyclopeptides provided to Scripps researchers have been used exclusively to generate data for submission to the FDA.

On July 18, 1996, plaintiffs filed suit against defendants alleging that Dr. Cheresh's discoveries infringe the '525 patent. Plaintiffs further allege that Scripps, as the employer, is liable for any patent infringement by Dr. Cheresh and that Merck has induced infringement by supporting Dr. Cheresh's research.

In August, 1996, Merck formed a team to evaluate EMD 85189 as a potential pre-clinical candidate for FDA testing. In October, 1996, Merck contacted the FDA for the first time to see who would handle a potential Investigational New Drug ("IND") application for an RGD peptide. On November 15, 1996, Merck's pharmaceutical steering committee officially nominated EMD 85189 for pre-clinical development to submit to the FDA. In April 1997, Merck switched the focus of its pre-clinical program from EMD 85189 to a variation of this compound, EMD 121974.

In their motion for partial summary judgment, defendants seek a declaration that all of defendants' research activities that culminated in Merck's EMD 85189 and EMD 121974 peptides, at least since September 1995, have not infringed plaintiffs' '525 patent as a matter of law, pursuant to 35 U.S.C. § 271(e)(1).

Plaintiffs oppose, arguing that defendants are ineligible for the § 271(e)(1) infringement exception. Plaintiffs further argue that even if defendants are found to be eligible for the exception, genuine issues of material of fact remain as to *when* that exception would begin to apply.

II. Legal Standard

Federal Rule of Civil Procedure 56(c) provides that summary judgment is appropriate if there is no genuine issue as to any material fact, and the moving party is entitled to a judgment as a matter of law. The movant has the initial burden of demonstrating that summary judgment is proper, *Adickes v. S.H. Kress and Co.*, 90 S.Ct. 1598, 1608 (1970). The burden then shifts to the nonmovant to show that summary judgment is not appropriate. *Celotex Corp. v. Catrett*, 106 S.Ct. 2548, 2553. To make such a showing, the nonmovant must go beyond the pleadings to designate specific facts showing that there is a genuine issue for trial. *Id.* However, in considering this motion, the evidence of the nonmovant is to be believed and all justifiable inferences are to be drawn in his or her favor, *Anderson v. Liberty Lobby Inc.*, 106 S.Ct. 2505, 2513 (1986).

III. Discussion

The first issue to be determined is whether defendants' conduct is eligible for the patent infringement "exception" contained in §271(e)(1). Defendants contend that since at least September, 1995, all of their research has been reasonably related to the development of information to be submitted to the FDA and is therefore exempt from patent infringement claims under §271(e)(1). In opposition plaintiffs argue that §271(e)(1) does not apply to defendants' research. Plaintiffs argue that §271(e)(1) only applies to cases involving FDA applications for "generic drugs" that seek to mimic an existing FDA-approved "pioneer drug" that already exists in the marketplace.

(A) The Patent Infringement Exception Under 35 U.S.C. §271(e)(1)

Under pre-1984 patent law, there were two unintended distortions of the typical 17-year patent term. While newly patented products were awaiting FDA approval, the underlying patent would continue to mature thereby reducing the number of protected years the patentee could sell the product in the marketplace once approved. At the same time, competitors were forced to wait until the 17 year patent period actually expired before initiating their own applications with the FDA to develop products based on the same technology. This would often result in several years of delay, effectively lengthening the patentee's protection from 17 to 20, even to 25 years. In 1984, Congress recognized this problem and amended §271(e)(1) of the patent code to provide:

> It shall not be an act of infringement to make, use, or sell a patented invention. . . . solely for uses reasonably related to the development and

> submission of information under a Federal law which regulates the manufacture, use or sale of drugs.

35 U.S.C. §271(e)(1). As a result, competitors can now utilize existing patented technology, while the original patent is still valid, so long as the use is "reasonably related" to the development of data to submit to a federal regulatory agency such as the FDA. *See Eli Lilly & Co. v Medtronic, Inc.*, 496 U.S. 661, 665-669 (1990).

Defendants argue that their research since September, 1995, has been "reasonably related" to the development of data to submit to the FDA and therefore is exempt from patent infringement claims pursuant to §271(e)(1). Plaintiffs, however, argue that §271(e)(1) should not apply in this case. Plaintiffs contend that §271(e)(1) applies only to "bioequivalence testing" typically performed in generic drug applications submitted to the FDA as "Abbreviated New Drug Applications ("ANDAs") and Paper New Drug Applications ("Paper NDAs"). ANDAs and Paper NDAs are based on a scientific demonstration that the applicant drug is equivalent to a 'pioneering drug' that has been previously approved by the FDA and is currently for sale in the marketplace. Plaintiffs argue that §271(e)(1) only applies to generic drug applications and not to defendants' proposed Investigational New Drug application. Notably, plaintiffs do not cite one case in support of their argument.

The court disagrees with plaintiffs' interpretation. Since the 1984 patent law revisions, courts have broadly interpreted §271(e)(1) to apply to the use of patented products to develop all applications for a drug or medical device that requires FDA premarket approval, *Eli Lilly & Co. v. Medtronic, Inc.*,

496 U.S. 661, 665-669 (1990). In *Eli Lilly* the Supreme Court held that so long as the use of a patented product is "reasonably related" to the development of information subject to regulation under the entire Federal Food, Drug, and Cosmetic Act ("FDCA") it is exempt under §271(e)(1). *Id.* at 666. The Court rejected a piece-meal application of §271(e)(1) to only certain types of drug applications or provisions under the FDCA. *Id.* at 673-674. Instead, the Court concluded that §271(e)(1) applies to all submissions under the FDCA Act.

Although the Ninth Circuit has not addressed the issue, the Federal Circuit recently confirmed this expansive reading of §271(e)(1), holding that "section 271(e)(1) makes no distinctions based upon the different FDA classes of medical devices or drugs." *Abtox, Inc. v. Exitron Corp.*, 1997 U.S. App. LEXIS 19975, at *29-30 (Fed. Cir. August 1, 1997). Furthermore, at least one district court has confirmed that the exemption applies to Investigational New Drug applications. *NeoRX Corp. v. Immunomedics, Inc.*, 877 F. Supp. 202, 204 (D.N.J. 1994).

Section 271(e)(1) was enacted to create 'a legal environment that would enable new, medically beneficial, cost-competitive products to reach the general marketplace . . . just as soon as the undistorted operation of the patent laws would permit." *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1272 (N.D.Cal. 1991), *aff'd*, 991 F.2d 808 (1993). Thus, Congress wished to afford the protection of §271(e)(1) to "every party who might be in a position to enter the general marketplace when the relevant patents expire." *Intermedics, Inc.*, 775 F. Supp. at 1274.

Plaintiffs argue that finding defendants eligible for §271(e)(1) relief in this case would destroy the value of plaintiffs' patents. However, even if defendants' FDA-related activities are exempt, assuming plaintiffs' patents are valid, plaintiffs can still exclude defendants from entering the commercial marketplace with an infringing peptide prior to the expiration of their patent. If defendants wish to commercially market an infringing peptide during the term of the patent, they will still have to negotiate a license with the plaintiffs. Thus, defendants would still have a strong incentive to seek licensing should they develop a successful FDA-approved product that could be marketed sooner than it would have under pre-1984 patent law. *See Abtox*, LEXIS 19975, at *23.

Plaintiffs argue that a broad application of §271(e)(1) would work a manifest injustice on all "small biotech firms" such as Plaintiffs herein by rendering useless all patents on drug development discovered by smaller biotech firms. Plaintiff's argument overlooks three critical points. First, even assuming a large pharmaceutical company is successful in creating a "pioneer drug" based on a biotech's patented technology under §271(e)(1), the pharmaceutical company would still need a license to legally sell it in the marketplace prior to the expiration of the patent.

Second, §271(e)(1) eliminates the necessity of a pharmaceutical company, large or small, having to seek numerous and expensive patent licenses that ultimately do not result in the approval of a pioneering drug. By applying §271(e)(1) to Investigational New Drug applications, the pharmaceutical companies can utilize a variety of patented technologies in their efforts to develop an approved pioneer or generic drug and then face the obstacles of either acquiring

the appropriate patent license or waiting until the underlying patent expires.

Finally, the statute itself is broad, it exempts making, using, or selling a patented invention reasonably related to the development and submission of information under a federal law without requiring the ultimate manufacture, use, or sale of an actual drug. Certainly, if Congress wished to prescribe using patent information for all Investigational New Drug applications, it could have done so in the plain wording of the statute. However, allowing the exemption to apply to a proposed Investigational New Drug application is consistent with Congressional intent to not artificially extend a patent's life beyond seventeen years. In fact, applying §271(e)(1) to cases such as this encourages research and development in an era of rapidly evolving science and technology. For these reasons, the court finds that defendants' conduct is eligible for the §271(e)(1) exception in this case.

(B) ***Material Issues of Fact Still Remain in This Case***

Having found that defendants are eligible for protection under §271(e)(1), the court must next determine whether any genuine issue of material fact remains as to *when* defendants' conduct became exempt under §271(e)(1). In making this determination, all justifiable inferences are to be drawn in plaintiffs' favor, *Anderson v. Liberty Lobby Inc.*, 106 S.Ct. 2505, 2513 (1986).

When determining whether an activity is exempt under §271(e)(1), the question is whether the defendants used the patented technology "solely for uses reasonably related to the development and submission of information" to the relevant federal agency. 35 U.S.C. §271(e)(1). The court must

apply an objective standard to determine whether it would "have been reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute to the generation of . . . information relevant to FDA approval." *Intermedics*, 775 F. Supp. at 1280.

Plaintiffs highlight that defendants' experiments conducted after September, 1995, have involved membranes of chicken eggs. These tests are also known as "CAM assays". Plaintiffs contend that the use of a chicken membrane, rather than a mammal membrane, renders the results inadequate for obtaining FDA approval for clinical trials. [*See* Goodman Depo. at 88-89 (P's Exhibit 20)]. Apparently, the FDA requires IND drug applications to include testing on mammals in order to secure approval for subsequent clinical testing on humans. [P's FDA Expert, Meyers Decl. ¶6,9]. While this may be true, it is reasonable for scientists to gradually build on their research as a project matures. There is no evidence before the court indicating that one starts testing with pioneering technology on mammal cells from day one. Rather, it appears to involve a gradual process that ultimately culminates in mammal call testing. Therefore the court finds that defendants' use of a chicken membrane, standing alone, does not create an issue of triable fact as to the scope of defendants' research.

Defendants argue that the September, 1995, "Research Funding and Option Agreement" entered into between Merck and Scripps created a detailed and specific program to bring EMD 85189 to clinical trials for FDA approval. Defendants allege that since that agreement, the research has significantly narrowed its focus to matters "reasonably related to the development" of data for submission to the FDA such that the research is protected under §271(e)(1) as a matter of law.

At oral argument, defendants argued that the September, 1995, agreement established the start of a "three year program" in which the defendants planned to initiate FDA approved clinical trials. However, the agreement nowhere indicates that the research would be geared solely to generate data for FDA submission. [Jonczyk Decl. Exhibit B]. In fact, there is limited mention of the FDA throughout the body of the agreement. For example, in the section detailing the general goals for each year of the proposed program, the FDA is only mentioned as part of the research goals for the third year. The agreement reads, "Year 3: Based an toxicological data, an IND will be filed together with clinical collaborators for cancer as well as eye disease. Any additional data required at that time will be gathered to satisfy the F.D.A." (*Id.* Exhibit B, p. 33 (emphasis added)]. Based on this language, the program does not appear to be geared toward FDA submissions until the third and final year of the program. This conflicts with defendants' contention that all research from September, 1995, was reasonably related to the development of data for FDA submission.

Furthermore, plaintiffs present deposition testimony that suggests that the scope of the September 1995 agreement was much broader then research strictly related to producing FDA data for EMD 85819. During a July 25, 1997 deposition of the Merck scientist in charge of collaboration between Merck and Scripps, Dr. Lukenbach testified that the agreement was actually broader than the previous Merck-Scripps collaborations and was intended to cover research on any compound, whether it was the EMD 85819 peptide, other peptides, non-peptides, or antibodies. [Lukenbach Depo. at 65, 70, 71, 100, 101 (P's Exhibit 19)]. This testimony conflicts with Merck's contention that as of September 1995, all research was reasonably related to the development of

data for the FDA, particularly as to EMD 85189, or its derivative, EMD 121974. Accordingly, the court finds that triable issues of fact remain as to the precise nature and scope of the September, 1995 agreement and whether that agreement marks the date on which all research was reasonably related to FDA purposes.

In addition, defendants' assertion that all work since September, 1995, has been directed toward generating data for submission to the FDA appears contradicted by the dates of certain key events by defendants. For example, the deposition of Merck's project manager, Dr. Noll, reveals that Merck did not even form a team to evaluate EMD 85189 as a potential pre-clinical candidate until August, 1996, two months after this lawsuit was filed. [*See* Noll Depo. at 26, 27 (P's Exhibit 18)]. Notably, Dr. Noll testified that the pre-clinical phase of the cyclic RGD peptide 85189 project did not begin until the steering committee granted its approval on November 15, 1996. Moreover, it was not until April, 1997 that Merck chose a derivative of EMD 85189, EMD 121974, for pre-clinical development and possible submission to the FDA. [Jonczyk Depo. Vol. II. at 62]. These events create a triable issue of fact as to precisely when defendants' research may have shifted from "general research" to "research reasonably related to the development of data for submission" to the FDA.

At oral argument, the defendants suggested that the court should grant partial summary judgment, at minimum, as of November, 1996, Defendants based this contention on Merck's official vote to approve EMD 85189 for pre-clinical research at that time. However, the mere fact that EMD 85189 was approved by Merck's steering committee for pre-clinical development in November, 1996, does not necessarily mean

that the entire scope of Dr. Cheresh's research suddenly became exclusively devoted to the development of data for FDA submission on that date. Defendants present no evidence that demonstrates that Dr. Cheresh altered the focus of his research in any way after November, 1996. It may well be the case that defendants' research was exempt in 1995, 1996, and 1997. However, on the evidence presented, a substantial factual dispute remains as to when the pre-clinical development of any RGD peptide would have been eligible for exemption under §271(e)(1).

To the extent that defendants argued during oral argument that there was no way that summary judgment could not be granted as to Dr. Friedlander, the court notes that Dr. Friedlander was neither a named party in the original Complaint nor the recently filed Amended Complaint. Therefore any arguments regarding the conduct of Dr. Friedlander are not material to the resolution of this summary judgment motion.

Moreover, although Merck has been attempting to bring the EMD 121974 peptide to market, they admit that they have been using other peptides, such as EMD 66203, and non-peptides, in conducting their research. (Lukenbach Depo. 75-76, (P's Exhibit 20)]. During a deposition, the head of Merck's organic chemistry department who monitors the relationship between Merck and Scripps stated that non-peptide experimentation is not necessary to carry out clinical work for the development of RGD peptides. [Jonczyk Depo. Vol. 11 at 97 (P's Exhibit 21)]. Because defendants contend that their research has related exclusively to developing FDA data for the 85189 and 121974 peptides, the court finds that the use of non-peptides raises an issue of fact as to whether defendants' post 1995 research has been "solely for uses

reasonably related to the development of information for submission" to the FDA 35 U.S.C. §271(e)(1) (emphasis added). In fact, plaintiffs suggest that the only reason that Merck has been using non-peptides, has been in an attempt to create their own new patentable technology that mimics plaintiffs' '525 patent on a non-peptide platform.

The court also finds conflicting issues of fact in the testimony of defendant Dr. Cheresh. In his signed declaration submitted with this motion, Dr. Cheresh claims that all of his research with cyclic peptides has generated data that relates to the eventual submission of information to the FDA [Cheresh Decl. 9-10]. However, this statement is contradicted by Dr. Cheresh's earlier responses to interrogatories regarding uses of RGD peptides in his scientific experiments which state "Dr. Cheresh's work . . . from 1985 to date, constitutes basic laboratory research undertaken for philosophical and scholarly gratification." [Responses to First Set of Interrogatories at 7, (P's Exhibit 23)]. Dr. Cheresh's declaration appears to also be contradicted by his National Institute of Health ("NIH") grant applications. During his deposition, Dr. Cheresh testified that the majority of the funding necessary to run his laboratory is obtained from NIH grants. [Cheresh Depo. Vol. 11, at 134]. However, Dr. Cheresh's grant application to the NIH never mentions Merck, the FDA, or the fact that he is conducting experiments to develop data to submit to the FDA. Although plaintiffs have not proven that Dr. Cheresh had a duty to disclose such facts in his NIH application, it nonetheless demonstrates the apparently conflicting positions that Dr. Cheresh has taken throughout this litigation. Issues of fact thus remain regarding the scope of Dr. Cheresh's research and his use of peptides and non-peptides since September, 1995. Based on the evidence submitted, the court cannot say as a matter of law

that Dr. Cheresh has been strictly conducting his research for FDA purposes, or alternatively for general scholarly gratification, or precisely when a shift in the focus of his research may have occurred.

Last, although defendants argue that all research since September, 1995 has been "reasonably related" to compiling data for the FDA, depositions of Merck scientists reveal that Merck, to date, has failed to compile any toxicological data that complies with "Good Laboratory Practice' ("GLP") requirements necessary for FDA submittal. [Jonczyk Depo, Vol. 11, 69-70]. At oral argument, defendants conceded that Dr. Cheresh's laboratory is not GLP certified and that GLP certified testing data will be required to gain FDA approval. While the lab results that have been compiled thus far will likely aid the defendants in their eventual submissions to the FDA, failure to abide by the FDA's strict GLP certification requirements is corroborative of plaintiffs' argument that the scope of defendants' research since September, 1995 has been general and not restricted to seeking FDA approval.

The court concludes that the lack of a clear indication that Dr. Cheresh's work was conducted, or will ever be conducted, under proper GLP certification argues in favor of a finding that it is unclear whether the research was reasonably related to FDA submission since September, 1995. Moreover, while the court acknowledges that the FDA accepts both GLP and non-GLP data in its review of Investigational New Drug applications, on the evidence presented, the court cannot determine as a matter of law precisely when defendants' research may have become "reasonably related" to compiling data for the FDA to qualify for protection under 35 U.S.C. §271(e)(1).

IV. *Conclusion*

In sum, the court finds that several genuine issues of material fact remain in this case. Defendants' motion for partial summary judgment under 35 U.S.C. § 271(e)(1) is therefore denied.

IT IS SO ORDERED.

9/9/97
Date

Chief Judge Judith N. Keep
United States District Court
Southern District of California

cc: all parties

APPENDIX 5 — EXCERPT FROM MERCK'S MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF ITS MOTION FOR JUDGMENT AS A MATTER OF LAW AT CLOSE OF PLAINTIFF'S CASE, DOCKET # 1051

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307 JMF (AJB)

INTEGRA LIFESCIENCES I, LTD., a Delaware corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,

Plaintiffs,

v.

MERCK KGaA, a German corporation,

Defendant.

AND RELATED COUNTERCLAIMS

MEMORANDUM IN SUPPORT OF MOTION BY MERCK KGaA FOR NEW TRIAL RE SECTION 271(e)(1) DEFENSE

POST-JUDGMENT MOTION NO. 2 OF 6

Date: November 13, 2000
Time: 10:30 a.m.
Ctrm: Hon. James M. Fitzgerald

INTRODUCTION

Merck KGaA ("Merck") moves for a new trial on the applicability of 35 U.S.C. Section 271(e)(1) ("the FDA Exemption") to each and every experiment that formed the basis for the claims that (a) it induced infringement by providing funds and the accused compounds to Drs. Cheresh, Friedlander and Storgard at The Scripps Research Institute ("Scripps") from August 1995 to December 1998, and (b) it directly infringed one of Plaintiffs' patents by importing the accused compounds into the United States after January 1, 1996.

The jury did not have a fair opportunity to consider the great weight of the evidence establishing the FDA. Exemption vis-à-vis the accused experiments, as that defense was only one of a myriad complex questions of patent validity and infringement addressed during a seven week trial. Furthermore, critical evidence, i.e., the Investigational New Drug Application ("IND") filed by the National Cancer Institute regarding Merck's cancer drug candidate, was improperly excluded from the trial. Moreover, the jury verdict form improperly combined sixteen categories of accused experiments, thus preventing the jury from evaluating independently each of the experiment categories accused of infringement. Finally, the jury instructions regarding the FDA Exemption did not fairly inform the jury of the meaning and scope of the exemption, while counsel for Plaintiffs severely prejudiced and confused the jury by making closing arguments that are contrary to law and that were not supported by any evidence at trial.

I.
MERCK IS ENTITLED TO A NEW TRIAL UNDER THE NINTH CIRCUIT STANDARD.

A motion for a new trial and a judgment as a matter of law are distinct motions guided by different standards. The standard for a motion for a new trial is less strict because a court may grant a new trial even if the verdict is supported by substantial evidence. *See Hanson v. Shell Oil Co.*, 541 F.2d 1352, 1359 (9th Cir. 1976), *cert. denied*, 429 U.S. 1074 (1977) ("The trial court may grant a new trial, even though the verdict is supported by substantial evidence . . . ."). The standard was laid out in *Moist Cold Refrigerator Co. v. Lou Johnson Co.*, 249 F.2d 246 (9th Cir. 1957), *cert. denied*, 356 U.S. 968 (1958):

> [H]aving permitted the jury to come to its conclusion on the facts, the trial judge then had the right, and indeed the duty, to weigh the evidence as he saw it, and to set aside the verdict of the jury, even though supported by substantial evidence, where, in his conscientious opinion, the verdict is contrary to the clear weight of the evidence, or is based upon evidence which is false, or to prevent, in the sound discretion of the trial judge, a miscarriage of justice. Id. at 256 (emphasis added).

The trial court, when assessing a motion for new trial, need not view the evidence in the light most favorable to the verdict winning party. *See Air-Sea Forwarders, Inc. v. Air Asia Co.*, 880 F.2d 176, 190 (9th Cir. 1989), *cert. denied*,

493 U.S. 1058 (1990). This distinction was explained in *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559 (Fed. Cir. 1996), *vacated on other grounds*, 520 U.S. 1111 (1997):

. . .

* * *

[6] . . . this defense, filed concurrently herewith, Merck has set forth in detail the voluminous and largely uncontradicted evidence supporting the defense. The same discussion, and supporting documentation, fully support this motion for a new trial.

C. The Form Of Verdict Improperly Prevented The Jury From Indicating Whether It Found One Or More Categories Of Experiments To Be Exempt.

A dozen trial witnesses testified specifically and distinctly why each of the accused categories of experiments is covered by the FDA Exemption.[2] Over the objection of Merck, the jury was given a verdict form that inquired only whether it found that all of the accused experiments were exempt under Section 271(e)(1).[3] As a result, even if the jury

2. Those witnesses included Drs. Cheresh, Friedlander, Storgard, Reisfeld, Lerner, Brooks, Laug, Bynum, Houston, Goodman, and Grimm and Mr. Armitage.

3. Merck forcefully objected to the verdict form proposed by Plaintiffs and adopted by the Court. The jury's verdict is attached as Exhibit A to the Declaration of M. Patricia Thayer in Support of (Cont'd)

concluded that fifteen of the sixteen categories were exempt, it had no opportunity to so indicate, and Merck, as well as the scientists at Scripps, have had to halt all investigations using the accused compounds.

This ambiguous form of jury verdict has forced Merck and Scripps to suspend experiments using the accused Merck [7] cyclic peptides in the United States. Research programs of clinical researchers like Dr. Friedlander and Dr. Storgard, have suffered accordingly. This is likely to cause untold harm to patients that might otherwise have received treatment involving the accused compounds for cancer, eye disease and arthritis. Moreover, the impact of the verdict on other scientists in this country, while not quantifiable, is nonetheless certain. This closely-watched, important case has sent the message that if a company engages in animal research, which everyone agrees is an essential predicate to the filing of an IND, it may potentially incur huge liability for patent infringement, or be enjoined.[4]

(Cont'd)
Motion for New Trial re Section 271(e)(1) Defense ("Thayer Decl."). Prior to and during the trial, Merck proffered several different verdict forms that included a chart separating the findings with respect to each category of accused experiments. *See, e.g.*, Exhibit B to the Thayer Declaration.

4. Even Plaintiffs' expert, Mr. Meyer, conceded that experiments to demonstrate efficacy, pharmacology, and mode of administration, and to select the most effective drug candidate, are undertaken by any rational drug company before filing an IND. Tr.

This unique, inscrutable verdict has sent a message to the scientific community that well-accepted preclinical drug research cannot proceed without the threat of a jury finding, years later, that one or several experiments were not sufficiently related to the FDA review process. Imposing such confusion and doubt on drug development in this country is contrary to the clear intent of Congress, embodied in 35 U.S.C. Section 271(e)(1), to encourage research and development of new drug products during the term of patents.[5]

* * * *

5. *E.g.*, *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1029 (Fed. Cir. 1997) ("Section 271(e)(1) supplied potential infringers . . . the benefits of an infringement shield to erase the de facto extension of the patent term caused by the requirement to await patent expiration before starting the tests for regulatory compliance"); *Telectronics Pacing Sys. v. Ventritex*, Inc., 982 F.2d 1520, 1525 (Fed. Cir. 1992) ("Congress must have intended to allow competitors to be in a position to market their products as soon as it was legally permissible"); *Smithkline Beecham Corp. v. Apotex Corp.*, 1999 U.S. Dist. LEXIS 7249 (N.D., Ill. 1999) (one of the purposes of the statute is to "make available more low cost generic drugs and to create new incentive for increased expenditures for research and development for certain products which are subject to pre-market approval"); *Abtox, Inc. v. Exitron Corp.*, 888 F. Supp. 6, 9 (D. Mass. 1995) (Congress intended that "the courts give parties some latitude in making judgments about the nature and extent of the otherwise infringing activities they would engage in as they sought to develop information to satisfy the FDA"); *NeoRx Corp. v. Immunomedics*, 877 F. Supp. 202, 205 (D.N.J. 1994) ("Congress clearly decided that it wanted potential competitors to be able to ready themselves, fully, during the life of the patent, to much of the commercial market place in a large-scale way as soon as the relevant patents expired").

APPENDIX 6 — EXCERPT FROM MERCK'S REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF ITS MOTION FOR JUDGMENT AS A MATTER OF LAW, DOCKET # 1110

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

No. 96-CV-1307 JMF (AJB)

INTEGRA LIFESCIENCES I, LTD., a Delaware corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,

Plaintiffs,

v.

MERCK KGaA, a German corporation,

Defendant.

AND RELATED COUNTERCLAIMS

REPLY MEMORANDUM IN SUPPORT OF MOTION BY MERCK KGaA FOR NEW TRIAL RE SECTION 271(e)(1) DEFENSE

POST-JUDGMENT MOTION NO. 2 OF 6

Date: December 15, 2000
Time: 10:30 a.m.
Ctrm: Hon. James M. Fitzgerald

[Commencing at page 2]

. . . supported a finding that the chick CAM experiments were nonexempt, the judgment allegedly would be the same. Opp. Br. at 5-6. That argument ignores the fact that the trial covered research unrelated to cancer which has been halted because of the verdict. Unlike the cancer studies, which reached the IND stage before trial and now proceed in human clinical trials, research on arthritis and eye disease was in the preclinical phase at the time of the verdict. Tr. 1598-99 (Storgard); 1882-83 (Friedlander). Because the verdict did not permit the jury to exonerate those experiments under the FDA Exemption, and because Scripps cannot risk yet another lawsuit claiming punitive damages,[2] it has no option but to terminate the research program using the Merck peptides.

II. MERCK IS ENTITLED TO A NEW TRIAL DUE TO INCOMPLETE, ERRONEOUS JURY INSTRUCTIONS.

Merck's rejected jury instructions properly asked the Court to interpret the statutory language, "reasonably related," and give the jury a context for applying the FDA Exemption to the facts.[3] Plaintiffs respond that the barebones instructions

2. The fact that this Court denied Plaintiffs' request for injunctive relief at this time is irrelevant. Nothing prevents Plaintiffs from suing again, and seeking treble damages and attorney fees, regarding present or future research on eye disease or arthritis.

3. Plaintiffs argue that it would be error to inform a jury about legislative history or intent, but they cite no case authority.

adopted by the Court were sufficient because they were based on the 1991 Intermedics case. However, the. . . .

[Ex. A, pp. 1-3, in Supp. App. at SA6]

* * * *

APPENDIX 7 — EXCERPT FROM MERCK'S MOTION FOR JUDGMENT AS A MATTER OF LAW AT THE CLOSE OF EVIDENCE, DOCKET # 978

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307

Trial Date: February 8, 2000

Trial Judge: James M. Fitzgerald
Motion Judge: Thomas J. Whelan

INTEGRA LIFESCIENCES I, LTD., a Delaware corporation, and THE BURNHAM INSTITUTE, a California not for profit corporation,

Plaintiffs,

vs.

MERCK KGaA, a German corporation,

Defendant.

* * *

[Commencing at page 16]

Exemption. *See Roche Prods., Inc v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984) (testing to prepare data for the FDA beyond the scope of Experimental Use Exemption) (superceded by statute). Based on the undisputed evidence and the proper reading of the law, the accused activities undertaken prior to 1995 should be deemed experimental use, exempt from patent liability.

B. The Court Should Grant Defendants JMOL That The Experiments Conducted After 1994 (Except Those Involving MMP-2) Are Exempt From Patent Infringement Under The FDA Exemption.

1. Section 271(e) (1) Is Broad And Flexible Intended By Congress And Construed By The Courts To Speed The Deyelopment Of New Human Drug

35 U.S.C. Section 271(e)(1) exempts from patent liability otherwise infringing uses of patented inventions if those uses are "reasonably related" to generating data for submission to the FDA. The exemption is a broad one. Order Denying Defendants' Motion For Partial Summary Judgment Re 35 U.S.C. §271(e), filed September 11, 1997 ("271(e) (1) Order") at 5. As this Court has held, the question is whether it would have been "reasonable, objectively, for a party in defendant's situation to believe that there was a decent prospect that the 'use' in question would contribute (relatively directly) to the generation of kinds of information that was likely to be relevant in the processes by which the FDA would decide whether to approve the product." *Id.* at 7 (citing *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991)).

APPENDIX 8 — JURY INSTRUCTION ON THE FDA EXEMPTION

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307 JMF (AJB)

INTEGRA LIFESCIENCES I, LTD.,
a Delaware corporation, and
THE BURNHAM INSTITUTE,
a California nonprofit corporation,

Plaintiffs,

v.

MERCK KGaA, a German corporation

Defendant.

AND RELATED COUNTERCLAIMS

JURY INSTRUCTIONS

As Given, March 16, 2000:

s/ James M. Fitzgerald
James M. Fitzgerald
United States District Judge

Jury Instruction No. 32

DEFENSE OF NON-INFRINGEMENT UNDER 35 U.S.C. §271(e)

Merck contends that it does not infringe or induce the infringement of any of the patents-in-suit, based upon the Food and Drug Administration, or "FDA" Exemption. To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

Each of the accused activities must be evaluated separately to determine whether the exemption applies.

Merck does not need to show that the information gathered from a particular activity was actually submitted to the FDA.

APPENDIX 9 — JURY VERDICT FORM, DOCKET # 995

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307-JMF (AJB)

INTEGRA LIFESCIENCES I, LTD., a Delaware corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,

Plaintiffs,

vs.

MERCK KGaA, a German corporation,

Defendant.

AND RELATED COUNTERCLAIMS.

VERDICT FORM

INTERROGATORIES TO THE JURY

I. INFRINGEMENT

1) Setting aside for this question the issue of the FDA Exemption, have **Plaintiffs** met their burden of proving by a preponderance of the evidence that **The Scripps Research**

Institute and/or Dr. Cheresh have infringed the following United States Patents:

A. United States Patent No. 4,792,525?

Claim 8? Yes X No ___

B. United States Patent No. 4,879,237?

Claim 4? Yes X No ___

Claim 8? Yes X No ___

C. United States Patent No. 5,695,997?

Claim 15? Yes X No ___

Claim 16? Yes X No ___

Claim 17? Yes X No ___

Claim 18? Yes X No ___

D. United States Patent No. 4,789,734?

Claim 1? Yes X No ___

Please proceed to question 2.

2) Setting aside for this question the issue of the FDA Exemption, have **Plaintiffs** met their burden of proving by a preponderance of the evidence that **Defendant Merck KGaA**

has infringed U.S. Patent No. 4,792,525 by importing into the United States after January 1, 1996, peptides which infringe Claim 8 U.S. Patent No. 4,792,525?

Yes X No __

Please proceed to question 3.

3) Setting aside for this question the issue of the FDA Exemption, have **Plaintiffs** met their burden of proving by a preponderance of the evidence that **Defendant Merck KGaA** has induced infringement of the following United States Patents:

A. United States Patent No. 4,792,525?

Claim 8? Yes X No __

B. United States Patent No. 4,879,237?

Claim 4? Yes X No __

Claim 8? Yes X No __

C. United States Patent No. 5,695,997?

Claim 15? Yes X No __

Claim 16? Yes X No __

Claim 17? Yes X No __

Claim 18? Yes X No __

D. United States Patent No. 4,789,734?

Claim 1? Yes X No __

Please proceed to question 4.

II. VALIDITY

4) Has **Defendant Merck KGaA** met its burden of proving by clear and convincing evidence that the following United States Patents are invalid:

A. United States Patent No. 4,792,525?

Claim 8? Yes __ No X

B. United States Patent No. 4,879,237?

Claim 4? Yes __ No X

Claim 8? Yes __ No X

C. United States Patent No. 5,695,997?

Claim 15? Yes __ No X

Claim 16? Yes __ No X

Claim 17? Yes __ No X

Claim 18? Yes __ No X

D. United States Patent No. 4,789,734?

Claim 1? Yes__ No X

Please proceed to question 5.

III. FDA EXEMPTION

5) Has **Defendant Merck KGaA** met its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA Exemption?

Yes__ No X

If you answered "Yes" to question 5, please sign and date the Verdict Form. If you answered "No" to question 5, please proceed to question 6.

IV. DAMAGES

6) If you found that **Defendant Merck KGaA** induced infringement of any of the patent claims in this case or directly infringed Claim 8 of the '525 Patent, and you also found that Merck did not meet its burden of proving by clear and convincing evidence that the infringed patent claims were invalid, you must decide the amount of damages adequate to compensate Plaintiffs or Merck's infringement.

What do you find, by the preponderance of the evidence, to be the damages to which **Plaintiffs** are entitled?

Answer: $15,000,000.00 (Fifteen Million U.S.)

Please proceed to question 7.

V. WILLFUL INFRINGEMENT

7) If you found **that Defendant Merck KGaA** induced infringement of any of the patent claims in this case, and you also found that Merck did not meet its burden of proving by clear and convincing evidence that the infringed patent claims in this case were invalid, then you must decide whether **Plaintiffs** met their burden of proving by clear and convincing evidence that Merck's inducement of infringement was willful.

Yes X No__

Please sign and date this form.

s/ [illegible] 3-17-2000
Foreperson Date

APPENDIX 10 — EXCERPT FROM RESEARCH AGREEMENT ("1988 AGREEMENT") BETWEEN SCRIPPS AND MERCK, EFFECTIVE JUNE 1, 1988

RESEARCH AGREEMENT

BETWEEN

SCRIPPS CLINIC AND RESEARCH FOUNDATION

AND

PHARMAFORSCHUNG der E. MERCK, DARMSTADT

[Commencing at page 4]

RESEARCH AGREEMENT

This Agreement is entered into this 29th day of November 1988, by and between SCRIPPS CLINIC AND RESEARCH FOUNDATION, 10666 North Torrey Pines Road, La Jolla, California 92037 ("SCRIPPS"), a California nonprofit corporation, and Pharmaforschung der E. Merck, Darmstadt, (E. MERCK) a general partnership under the laws of the Federal Republic of Germany, with respect to the facts set forth below.

RECITALS

Whereas SCRIPPS is engaged in scientific biomedical and biochemical research, including research relating to the use of peptides and/or antibodies that perturb cell adhesion for the treatment of cancer, wound healing, and angiogenesis.

Whereas SCRIPPS has the exclusive right to grant a license in and to the invention subject only to any non-exclusive rights of the U.S. Government, resulting from Government funding, for the Government to use the invention for its own purpose; and

Whereas E. MERCK is engaged in research and development of health-care products for diagnosis and therapy in man; and

Whereas SCRIPPS is interested in further research and evaluation of such peptides and desires to conduct such a research program with E. MERCK; and

Whereas E. MERCK desires to provide certain funding as part of Scripps Research activities related to cell adhesion in human metastatic disease, wound healing, and angiogenesis.

Whereas SCRIPPS desires to grant E. MERCK an option to an exclusive, worldwide right and license to develop and market diagnostic and therapeutic products which may arise from such research.

NOW, THEREFORE, in consideration of the mutual covenants and conditions outlined herein, SCRIPPS and E. MERCK hereby agree as follows:

ARTICLE I. DEFINITIONS

1.1 Scripps Proprietary Property. The term "Scripps Proprietary Property" shall mean any and all technology, now existing or hereafter arising in which SCRIPPS shall have a proprietary interest, including without limitation any idea, data, know-how, technique, method, process, use, composition, skill, confidential information, trade secret or configuration of any kind, whether or not any such information would be enforceable as a trade secret, the . . .

* * *

APPENDIX 11 — EXCERPT FROM RESEARCH FUNDING AND OPTION AGREEMENT ("1995 AGREEMENT") BETWEEN SCRIPPS AND MERCK, EFFECTIVE JULY 1, 1995

[Cover Sheet]

RESEARCH FUNDING AND OPTION AGREEMENT

by and between

THE SCRIPPS RESEARCH INSTITUTE

and

MERCK KGaA

[Pages 2-12 of the 1995 Agreement Omitted]

* * *

[EXHIBIT A TO RESEARCH FUNDING AND OPTION AGREEMENT ("1995 AGREEMENT")]

Scripps/E. Merck Program on Angiogenesis

Principal Investigator: David A. Cheresh, Ph.D.
Revised June 1995

[Tables of Contents
Intentionally Omitted]

INTRODUCTION

Angiogenesis in cancer and human disease

Solid tumor cancers account for over 600,000 new cases of cancer in the United States each year. While a few malignancies are amenable to chemotherapy or radiation treatment, many cancer patients have low five year survival rates. Cancer deaths can be caused by a variety of mechanisms, including tumor recurrence due to the development of resistance to anti-cancer therapeutics or the poor penetrance of drugs into tumors, toxicity from harsh anti-cancer therapies, or metastatic spread of tumors to numerous or inoperable sites through the tumor associated vasculature (Fraumeni, J., et al, 1992). The growth and spread of cancer has been suggested since the early 1970's to depend on the development of a vasculature (Folkman, J., 1971).

Angiogenesis, or neovascularization, is the process by which new blood vessels are derived from pre-existing vessels. Endothelial cells from existing blood vessels begin to migrate, proliferate, and form lumens as they respond to angiogenic factors in their environments. Normally, angiogenesis occurs only during the development of an organism (when it is called vasculogenesis) and during processes of wound healing and inflammation, when increased oxygenation and delivery of nutrients are needed to speed recovery of the injured tissue. Angiogenesis also occurs during menses. The aberrant growth of new blood

vessels, however, plays a significant role in many diseases which include solid tumor cancers, macular degeneration and diabetic retinopathy (the leading causes of blindness in adults), rheumatoid arthritis, psoriasis and inflammatory bowel disease (Auerbach, W. and Auerbach, R., 1994). Together these disease afflict more than five million Americans per year.

Tumors induce angiogenesis

Cancers begin as small populations of aberrant cells which divide more rapidly than neighboring normal cells. In order to extend beyond the small size of one cubic millimeter, solid tumors establish their own blood supplies by encouraging the growth of new blood vessels into the tumor tissue (Folkman, J., 1971; Gimbrone, M., et al, 1972). In the absence of a blood supply, oxygen and nutrients cannot penetrate to the tumor's core. Once the tumor vasculature is established, however, solid tumors receive the nutrients which enable them to expand and metastasize through the newly established vasculature. In fact, by the time that tumors are detectable, they have already established a vasculature and many have metastasized (Folkman, J., 1992).

One of the most significant consequences of angiogenesis in cancer is the spread of the cancer through the vasculature (metastasis). Metastases arise from tumor cells which enter the tumor's own vasculature to be carried to local and distant sites where they create new tumors (Blood, C.H. and Zetter, B.R., 1990). In fact, the degree of angiogenesis in a tumor s prognostic of metastatic potential and hence a poor therapeutic outcome, particularly in breast and prostate cancer

(Weidner, N., et al, 1991; Weidner, N., e: al, 1992; Gasparini, G., et al, 1992; Hayes, D.F., 1994; Weidner, N., et al, 1993) and in melanoma (Graham, C.H., et al, 1994).

Angiogenesis in eye disease

The vast majority of blinding eye diseases (including diabetic retinopathy, macular degeneration, retinopathy of prematurity, rubeotic glaucoma and pathological myopia) are characterized by the growth of new blood vessels in the retina and iris in response to angiogenic factors elaborated as a consequence of retinal ischemia. (White, P., 1960, Patz, A., 1980). If the growth of new blood vessels in the eye could be inhibited in these diseases, we could significantly reduce the visual morbidity associated with them. While significant progress has been made in identifying a variety of factors that promote and inhibit angiogenesis (Wiedemann, P., 1992; Aioelio, et. al., 1994) no treatment is currently available to specifically inhibit ocular neovascularization. Laser photocoagulation has proven effective in preventing severe visual loss in subgroups of high risk diabetic patients, but the overall 10 year incidence of diabetic retinopathy remains essentially unchanged. We have extensive preliminary data that demonstrates nearly complete inhibition of cytokine-induced ocular angiogenesis in animals treated with antagonists of the integrin $\alpha_v\beta_3$. The treatment does not affect pre-existing blood vessels and appears to be without ocular toxicity.

Angiogenesis in inflammation

Angiogenesis plays a major role in the progression and exacerbation of a number of inflammatory diseases. Psoriasis, a disease which afflict 2 million Americans, is characterized by significant angiogenesis. In rheumatoid arthritis and osteoarthritis, the blood vessels of the joint synovial lining undergo angiogenesis, which leads to an influx of lymphocytes and to the destruction of cartilage and bone. Angiogenesis also plays a role in chronic inflammatory diseases such as ulcerative colitis and Crohn's disease as well as in the progression of atherosclerosis.

Mechanisms of angiogenesis

The mechanisms of angiogenesis have been partially elucidated. Angiogenesis requires the activation of normally quiescent endothelial cells by secreted growth factors. Like oxygen-starved retinal cells, tumors secrete growth factors. Tumor secreted growth factors, such as basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), vascular endothelial cell growth factor (VEGF), and interleukin 8 (IL-8), induce the proliferation of and migration of endothelial cells toward the site of secretion (Klagsbrun, M., 1992; Plate, K.H., 1992; Smith, D.R., et al, 1994). Some of these factors (e.g., bFGF) are produced in such large amounts in cancer that their elevated levels in the blood may be prognostic of a poor therapeutic outcome (Nguyen, M., et al, 1994). Growth factor stimulation of endothelial cells also plays a role in psoriasis (Nickoloff, B.J., et al, 1994) and rheumatoid arthritis (Koch, A.E., et al, 1992).

Migration of endothelial cells into tumors or into regions of the eye, skin or synovium in response to growth factor secretion, requires their adhesion to proteins of the extracellular matrix, which include vitronectin, fibronectin, laminin, and collagen (Brooks, P., et al, 1994a; 1994b). Cellular adhesion to and migration through the extracellular matrix depends on a divalent cation-dependent family of cell adhesion proteins termed integrins (Cheresh, D., 1993). Integrins are present on most cell types, including neoplastic cells, platelets, leukocytes, fibroblasts and epithelial cells. These heterodimeric cell surface adhesion receptors play roles in blood clotting, wound healing, inflammation and development (Hynes, R.O., 1992). Integrins are composed of alpha and beta subunits that together form a ligand binding pocket to interact with small peptide regions of extracellular matrix proteins (often the tripeptide sequence Arg-Gly-Asp). Migration through the extracellular matrix also requires the expression and action of extracellular matrix degrading enzymes, such as collagenases, to clear a path for cellular movement (Folkman, J., 1992).

The search for angiogenesis inhibitors

Because angiogenesis is a fundamental process in adult blindness, in the development and spreading of cancer, and in diseases of chronic inflammation such as psoriasis and rheumatoid arthritis, a specific inhibitor of angiogenesis has long been sought by the medical community.

Each step in the activation and migration of endothelial cells suggests a potential strategy for the prevention of angiogenesis in the treatment of cancer and eye disease,

although efforts to date have focussed largely on the treatment of cancer. Neutralization of the endothelial cell growth factors produced by tumor cells or the inhibition of their interaction with endothelial cells are possible strategies that are currently under investigation (Folkman, J. and Ingber, D., 1992). Function-blocking antibodies directed against interleukin 8 (Smith, D.R., et al, 1994), basic fibroblast growth factor (Sakaguchi, M., et al, 1998; Reilly, T., et al, 1989; Abe, T., et al, 1993, Siuossat, T., et al. 1993) or vascular endothelial growth factor (Kim, K.J., et al, 1993) were effective in suppressing angiogenesis and tumor growth in animal models. Since many growth factors can be produced by diverse tissues throughout the body or by a single tumor, targeting growth factors and their receptors is not likely to be an effective therapeutic strategy.

Other reagents that inhibit endothelial cell proliferation include fumagillin and its less toxic analogue, AGM-1470 (also named TNP 470; Inger, D., et al, 1990). AGM-1470 inhibits endothelial cell proliferation (as well as that of other cell types) by blocking the G0 to G1 transition (Antoine, N., et al, 1994). AGM-1470 has displayed anti-tumor and anti-metastasis effects in several studies of tumorigenicity in animal models (Yanase, T., et al, 1993; Takamiya, Y., et al, 1993; Brem, R., and Folkman, J., 1993). Although AGM-1470 (which is currently in phase I clinical trials sponsored by Takeda Abbott Pharmaceuticals) has displayed anti-angiogenic activity in animal models, it has not been effective in Phase I clinical trials and has reportedly exhibited retinal, hepatic, and brain toxicities (Wilson, J.T., and Penar, P.L., 1994; Pluda, J.M., et al, 1994). Similarly, although thalidomide inhibits angiogenesis (D'Amato, R.J., et al,

1994), it is a potent teratogen. Another drug in clinical trials for cancer angiogenesis, carboxy-amino-imidazole (in Phase I clinical trials sponsored by the National Cancer Institute) is an inhibitor of the calcium influx component of the cell signalling pathways that are required for the proliferation of most cells (Alessandro, R., et al, 1991).

Inhibitors of protease secretion or function, such as the drugs minocycline (a collagenase inhibitor; Folkman, J. and Ingber, D., 1992), plasminogen activator inhibitor (PAI) and tissue inhibitor of metalloproteinase (TIMP) are under study for their potential as cancer therapeutics (Auerbach, W. and Auerbach, R., 1994). Other drugs such as platelet factor 4 (PF4) and thrombospondin which have an unknown mechanism of action are also under investigation as angiogenesis inhibitors (Folkman, J. and Ingber, D., 1992). Although PF4 induced tumor shrinkage in a phase II clinical trial in Kaposi sarcoma sponsored by Repligen, it must be delivered locally as it is rapidly neutralized by adsorption to heparin in the blood stream (Staddon, A., et al, 1994). Thus PF4 is of limited use in treating most cancers. Another new inhibitor of angiogenesis, angiostatin, which is a fragment of plasminogen, is also a molecule with an uncharacterized mechanism of action (O'Reilly, M., et al, 1994).

Although four drugs are in clinical trials for angiogenesis in cancer, they appear to lack the specificity of action, safety or appropriate biodistribution necessary to be good cancer therapeutics. There are no drugs currently in clinical trials or on the market for the therapy of human blindness caused by neovascularization; laser therapy is the only treatment at present and is of limited effectiveness. Hence, there is clear

need for continued development of potent and specific angiogenesis inhibitors.

Role of the integrin $\alpha_v\beta_3$ in angiogenesis

One of the most promising new angiogenesis inhibitors is a highly specific antibody or peptide inhibitors, of the cell surface protein known as the integrin $\alpha_v\beta_3$ or the vitronectin, receptor (VNR). As one of the integrin family of adhesion receptors, VNR or integrin $\alpha_v\beta_3$, depends on divalent cations and alpha/beta dimer association for function. VNR is the most promiscuous of integrins in that it can mediate cellular adhesion to and migration on vitronectin, fibronectin, fibrinogen, von Willebrand Factor, osteopontin, laminin, denatured collagen, and adenovirus penton base (Cheresh, D., 1987; Cheresh, D., et al, 1989; Hynes, R., 1992; Leavesly, D., et al, 1992; Cheresh, D., 1991). $\alpha_v\beta_3$ is expressed on a restricted population of cells, including proliferating endothelial cells and smooth muscle cells, malignant but not benign, melanoma and glioblastoma (Gladson, C. and Cheresh, D., 1991).

Attachment of VNR expressing cells to extracellular matrix proteins containing an RGD tripeptide sequence can be prevented by RGD peptides and by LM609, an $\alpha_v\beta_3$ complex specific function blocking murine monoclonal antibody. This antibody, LM609, prevents the angiogenic properties of endothelial cells in response to basic FGF, TNF alpha and tumor-secreted (Brooks, P., et al, 1994a; 1994b) and eye-secreted (Friedlander, M., et al, in preparation) growth factors during angiogenesis. The growth of new vasculature into tumor tissue (Brooks, P., et al; 1994a; 1994b)

or in the eye (Friedlander, M., et al, in preparation) is dependent upon the attachment of vascular endothelial cells to extracellular matrix proteins via the vitronectin receptor (VNR).

High levels of expression of the vitronectin receptor (VNR), but not of other integrins, are induced during wound healing but only on newly derived blood vessels (Clark, R., et al, 1994). VNR expression is also induced by growth factors in animal models of angiogenesis, such as the chick chorioallantoic membrane model and by tumor-secreted growth factors on proliferating vascular endothelial cells in all solid tumor tissues (Brooks, P., et al, 1994a; Brooks, P., et al, 1994b; Sepp, N., et. al, 1994). Expression of VNR is also observed during experimentally induced neovascularization in the eye, and during human neovascular eye diseases such as macular degeneration and diabetic retinopathy (Friedlander, M., et al, in preparation). In contrast, VNR is not highly, if at all, expressed on non-proliferating endothelium and is not expressed on most cells of the body, (Hall, W. and Varner, J., in preparation). Similarly, VNR is not expressed in the non-diseased eye (Brem, R., et al, 1994) nor on diseased eye which exhibit no signs of neovascularization (Friedlander, M., et al, in preparation). Hence VNR is an excellent potential target for anti-angiogenic strategies in the management of solid tumor cancer and blindness as well as other diseases involving excessive neovascularization, such as rheumatoid arthritis and psoriasis.

A highly specific, antagonist of VNR the antibody LM609 (Cheresh, D., 19877), prevents angiogenesis and

inhibits tumor growth and metastasis in animal models by inducing apoptosis of primarily endothelial cells (Brooks, P., et al, 1994b). In the absence of proliferating endothelial cell attachment to the substratum through the $\alpha_v\beta_3$ integrin, DNA fragmentation and apoptic morphologies are rapidly induced (Brooks, P., et al, 1994b). Integrin-ligand interactions are required for cell survival of all primary and some stored transformed cells (Meredith, J, et al, 1993; Montgomery, A., et al, 1994). Inhibition of angiogenesis by LM609 or a cyclic peptide antagonist of VNR leads to tumor shrinkage and complete necrosis by eliminating the nutrient supply (Brooks, P., et al. 1994b). LM609 also inhibits new blood vessel growth in the rabbit corneal pocket eye angiogenesis model, a choroidal angiogenesis model and an iris intraocular melanoma model (Friedlander, M., et al, in preparation). By binding only to sites of neovascularization *in vivo*, LM609 and cyclic peptide antagonists of VNR are excellent drug candidates for anti-angiogenic therapies.

Role of integrin $\alpha_v\beta_5$ in a novel pathway of angiogenesis

Recent evidence suggest that there may be two cytokine-dependent pathways of angiogenesis and these are defined by their dependency on distinct vascular cell integrins. Angiogenesis in the rabbit cornea or chick chorioallantoic membrane induced by bFGF or TNFa depends on $\alpha_v\beta_5$ (as shown above) while angiogenesis initiated by VEGF, TGFa or phorbol ester depends on $\alpha_v\beta_5$. Antibody antagonists of each integrin selectively block one of these pathways while a cyclic peptide antagonist of each integrin (RGDfV) of both integrins blocks angiogenesis stimulated by each cytokine tested. These pathways are further distinguished by their

sensitivity to calphostin C, a potent inhibitor kinase C that selectively blocks angiogenesis potentiated by $\alpha_v\beta_5$ but not $\alpha_v\beta_3$.

GOALS AND SPECIFIC AIMS

Overall Goal: To develop specific angiogenesis inhibitors based on antagonists of vascular cell integrin function for the treatment of human diseases.

Specific Aims:

1) To expand the use of currently available models of cancer-induced and ocular angiogenesis and to develop additional models of cancer-induced angiogenesis such as the rabbit VX2 carcinoma. These models are designed with the intention to examine the efficacy of E. Merck and TSRI-derived angiogenesis inhibitors. These models are in operation and have been fully approved by our animal right committee. Integrin antagonists will be tested for efficacy, pharmacokinetics, biodistribution and toxicity in these models.

2) To extend our collaboration to Dr. K.C. Nicolaou, Chairman of the Chemistry Dept at TSRI, who will design specific non-peptide mimetic antagonists of integrins in $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$. These compounds will be examined in purified receptor assays, cell adhesion assays and angiogenesis models in vivo. Based on results obtained in these models, the chemical structures of these compounds will be modified to obtain the most potent, specific, non-toxic inhibitors of angiogenesis in vivo.

3) To examine the molecular role of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ in angiogenesis in response to specific cytokines such as bFGF, VEGF, TNFa, and TGFa. This will involve both in vivo and in vitro analysis of vascular cell biological activity. We will examine the role of integrin antagonists on vascular cell signal transduction, invasion, proliferation, differentiation and apoptosis.

4) To examine a wide variety of human tumor tissue for the expression of angiogenic cytokines and integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. This information will establish whether certain types of cancer might be more susceptible to blockage of angiogenesis with antagonists of $\alpha_v\beta_3$ or $\alpha_v\beta_5$. These studies will be performed in collaboration with Dr. Malcolm Mitchell at the University of California San Diego who will provide access to clinical biopsy material and assist in identifying integrins and cytokines in these tissues. He will offer clinically relevant advice pertaining to tumor studies as they progress.

5) To explore other disease models in which angiogenesis and $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin antagonists may play an important role. This will include an analysis of cytokine and integrin expression in inflammatory tissues such as rheumatoid arthritis, and psoriasis. We will examine the effect of integrin antagonists in a rabbit model of arthritis

CURRENT IN VIVO MODELS AT SCRIPPS

1) Chick CAM embryo model. To investigate angiogenesis in response to recombinant cytokines and human tumor fragments. This model will be used to assess the role of

angiogenesis inhibitors on primary tumor growth and spontaneous pulmonary and hepatic metastasis of human tumors. Also, this model will allow us to examine whether individual cytokines potentiate angiogenesis via distinct integrins such as $\alpha_v\beta_3$ and $\alpha_v\beta_5$.

Advantages: Allows for the rapid examination of angiogenesis in three days or tumor growth and metastasis in seven days. Also, this model is relatively inexpensive and may be useful as an initial screen to assess the relative potency of inhibitors. This model does not require separate animal facilities. Allows for the isolation of vascular cells directly from the CAM for biochemical and biological analysis, in vitro as previously described by Brooks et al. Cell, 1994. Monoclonal and peptide antagonists of human integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ recognize these receptors in the chick. Allows for topical or systemic testing of inhibitory compounds.

2) Mouse/human chimeric model. This model utilizes SCID mice transplanted with full thickness human skin. This model will be used to examine human tumor growth and the role of angiogenesis in this process. This model depends on the growth of human blood vessels in the transplanted skin. In addition, we will examine the role of recombinant cytokines to stimulate human vascular growth and the role of integrins in this process.

Advantages: This models allows one to examine human angiogenesis in human tissue in response to a human tumor or recombinant cytokines. This model allows for immunohistochemical analysis of human blood vessels during their invasion into human tumors and should allow

the identification of relevant adhesive ligands involved in angiogenesis of human tumors. This model will also enable an assessment of the specifiic cytokines involved in various human tumor-induced angiogenesis. It will also enable an examination of the involvement of particular integrins in angiogenesis stimulated by specific recombinant cytokines.

3) Rabbit cornea. This model is classically used by investigators for the development of angiogenesis antagonists as possible therapeutics. This model will be used to examine angiogenesis induced by distinct cytokines, such as bFGF, VEGF and TNFa or tumors as well as the effectiveness of integrin antagonists in preventing the process.

Advantages: This model is a classic preclinical model that has been used by a wide number of investigators to test the therapeutic index of anti-angiogenic compounds. It is easy-to monitor, and we have established a method for precise quantification of angiogenesis. This model has relevance for ocular angiogenesis. A control and experimental compound can be examined simultaneously in the same animal (left and right eye, respectively). This model can also serve to test topical, intraocular and intravascular routes of treatment. Antibodies and peptides antagonists to human integrins react well with the rabbit.

ANIMAL MODELS UNDER DEVELOPMENT AT TSRI

1) Rabbit VX2 carcinoma. This is an experimental model of tumorigenicity and metastasis in which a rabbit carcinoma cell line (VX2) is transplanted subcutaneously into the same species of rabbit from which the cell line was derived. Within

two weeks, palpable tumors are formed. This model has been used previously to evaluate the effects of anti-tumor agents. Tumor dimensions before and after administration of anti-αv integrin and control reagents by an intravenous or other route will be determined. After treatment, tumors will be surgically removed and weights determined. Histological analysis of treated tumors will be performed.

Advantages: This is a reproducible model of tumorigenicity and metastasis in a mammalian species with demonstrated cross-reactivity of anti-αv, integrin reagents. It also utilizes the same species that will be used for pharmacokinetics, biodistribution and toxicology studies and will permit optimization of angiogenesis antagonism strategies. Useful for evaluation of efficacy of anti-$\alpha_v\beta_3$ reagents as well as for treatment regimen determination.

2) Spontaneous cancer in dogs (melanoma, breast, osteosarcoma) and cats (breast). Animals with tumors will be treated with anti-αv integrin and control reagents. Tumor size will be evaluated before and after treatment by ultrasound imaging techniques.

Advantages: Dog and cat αv integrins cross-react with anti-αv integrin reagents. Spontaneous tumors in animals are the closest representatives to human spontaneous tumor disease. These studies in larger mammalian species will be useful for further determination of treatment regimens that may be appropriate in humans.

3) Antigen or adjuvant induced arthritis in rabbits. Injection of lipopolysaccharide, albumin in complete Freund's adjuvant or cytokines (e.g., IL-S, TNFa) into the knee joint of rabbits induces arthritic symptoms which include swelling, angiogenesis and edema within 7-14 days. After administration of anti-αv integrin and control reagents, joint size and temperature will be evaluated-followed by histological analysis for number of blood vessels and lymphocytes per unit area as well as extent of cartilage and bone degradation.

Advantages: This is a rapid, inducible model of a species with demonstrated cross-reactivity of anti-αv integrin reagents. This model will permit evaluation of these anti-angiogenic reagents for their efficacy in ameliorating the symptoms of arthritis.

ROLE OF SCRIPPS INVESTIGATORS

The Scripps Research institute will initiate an in depth angiogenic program to investigate the role of integrin antagonists on diseases associated with angiogenesis such as solid tumor growth and metastasis, adult blindness, inflammatory disease, stroke and neointimal thickening after angioplasty. The structure of this program will involve a scale-up and extension of the long standing collaborative funding arrangement with the Cheresh laboratory. However, we plan to utilize the strengths of TSRI and to involve two other groups, headed by Martin Friedlander, M.D., Ph.D and K.C. Nicolaou, Ph.D. In addition we will work closely with Beth Ford D.M.V. who heads the TSRI animal facilities (see letter of collaboration). She will assist us with all phases

of these studies including the arrangement of canine spontaneous tumors.

The benefits of this TSRI program are several fold. First, we have in place various in vitro and in vivo models to evaluate the specificity, efficacy and toxicity of integrin antagonists as potential anti-angiogenesis drugs. The Cheresh laboratory is widely recognized as a leader in integrin biology as well as angiogenesis. Second, Dr. Friedlander provides expertise in receptor cell biology and biochemistry, as well as angiogenesis and neovascular eye disease. He is a qualified ophthalmologist with clinical specialty training in virreoretinal diseases and a clinical practice largely devoted to proliferative vascular eye disorders such as diabetes and macular degeneration. Third, we will collaborate closely with Dr. K. C. Nicolaou, to design and synthesize, non-peptide integrin in antagonists for analysis in our models. Dr. Nicolaou is among the most respected and capable synthetic organic chemists in the world. He recently reported the complete synthesis of Taxol. Forth, novel basic research discoveries and chemical compound discovered under this agreement may provide additional exciting new drug leads for diseases characterized by angiogenesis. Finally, this program is an extension of our previously highly successful agreement between Scripps and E. Merck.

COLLABORATION BETWEEN SCRIPPS AND E. MERCK

The goal of this program will be to take advantage of the strengths of E. Merck and Scripps to best develop integrin antagonists as angiogenesis inhibitors. Thus, compounds

designed and synthesized at E. Merck will be directly tested at Scripps. For example, we will test for integrin binding in vitro and then assess each compound in a series of animal models. We will utilize the chick CAM, SCID mouse and rabbit corneal model initially. We will examine each compound for half-life, toxicity and efficacy. We will send E. Merck samples of blood taken from animals at various times post-injection which will then be subjected to quantitative and qualitative analysis.

We will employ a highly trained laboratory manager who will prepare monthly progress reports outlining the progress our studies. We will make at least two trips per year to E. Merck to discuss the studies in depth and to decide how best to proceed. All new discoveries will be disclosed through our technology transfer office for potential licensing by E. Merck as has been done in the past. We would welcome E. Merck scientists to visit our facilities and assist in the technical and conceptual design of this program.

E. Merck is in position to scale-up the production and purification of any lead compounds developed here. This will allow further testing and analysis in our models for any compounds that show promise.

TIME SCALE FOR PROPOSED STUDIES:

We propose a three year time frame to develop this program. It is anticipated that within the third year clinical trials will begin and patent approval will be granted.

Year 1: We will initiate additional models and begin testing the E.M. peptide 66203 and Mab LM609 for efficacy. Pharmacokinetics and toxicity testing will be initiated in rabbits. We will test the role of $\alpha_v\beta_5$ antagonist Mab P1F6 in VEGF verses bFGF-induced angiogenesis. Tumor biopsies and normal tissues will be examined by immunohistochemical for presence of $\alpha_v\beta_3$, $\alpha_v\beta_5$ and various angiogenic cytokines, such as VEGF, bFGF, TNF and TGFa. Petidometics produced in K.C. Nicolaou's laboratory will be tested in cell adhesion experiments, to determine rank order, potency toward $\alpha_v\beta_3$ or $\alpha_v\beta_5$. This will also be performed for all E. Merck derived compounds. Each structure will be assessed with peptide and antibody controls, in in vivo models of angiogenesis chick CAM, SCID mouse and rabbit eye.

Year 2: Studies from year 1 will continue. All in vivo models will be fully operational. We will begin testing second, third and fourth generation peptides and mimetics for efficacy, safety and pharmacokinetics. Based on evidence obtained in year 1, clinical contacts for specific cancer indications will be developed. Also; under the direction of Dr. Friedlander, ocular trials will be planned. We anticipate that compounds previously optimized for potency will require chemical modifications to increase half-life. These will then be tested in all relevant models. Biochemical studies will be performed to characterize vascular cell signaling via integrins $\alpha_v\beta_3$ versus $\alpha_v\beta_5$. Antagonists developed above will be tested-for their impact on these signaling events.

Year 3: Based on toxicological data an IND will be filed together with clinical collaborators for cancer as well as eye disease. Any additional data required at that time will be

gathered to satisfy the F.D.A. Patent approval will likely depend on our ability to support claims regarding mimetics. Thus, lead compounds will be used to generate data required by the patent examiner deemed necessary for patent approval. Clinical trials (phase I/II) for specific cancer indications and macular degeneration will begin.

* * *

[EXHIBIT B TO RESEARCH FUNDING AND OPTION AGREEMENT ("1995 AGREEMENT")]

Attachment to

Research Agreement

between

The SCRIPPS Research Institute, La Jolla

and

Preclinical Research MERCK KGaA, Darmstadt

Scope of Research

Field of collaborations:

Diagnosis, prevention and treatment of any disease, state or condition in humans and/or animals related to function of cell adhesion,

like cancer, angiogenic disorders, inflammatory diseases, osteoltic diseases, microbial infections and/or wound healing.

Preclinical research and development in cell adhesion, targeting directly or indirectly the function of adhesion receptors, especially integrins.

Discovery and development of molecules, like peptides, proteins, peptidomimetics, or non-peptidic compounds, which modulate – promote or inhibit - cell adhesion.

Present focus of cooperation:

Exploration and characterisatian of molecules of diagnostic or therapeutic value, which are ligands of αv and/or β3-integrins. These molecules might be peptidomimetic or non-peptidic compounds of low or high molecular weight.

Search and determine of physiological and patho-physiological function of αv, and β3-integrins.

In vitro and in vivo testing, related to cell adhesion.

Goal is successful performance of necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials.

Responsibility and aims of laboratories presently involved in cooperation at TSRI:

Dr. David Cheresh:

Consultancy for EMD to determine the function, cellular regulation and signal transduction of αv and β3-integrin,

testing of EMD-derived and TSRI-derived compounds as well as compounds from other sources,

and to determine in vitro and in vivo the function and activity of the compounds tested,

Provision of in vitro and in vivo testing capacity for more than 100 compounds per year selected by EMD for

- development and/or use of isolated integrins in binding inhibition assays, momentarily focusing on $\alpha_v\beta_3$ and $\alpha_v\beta_5$,
- testing of compounds in integrin dependent cell attachment and migration assays, momentarily focusing on tumor cells and endothelial cells,
- use of inhibitors in chick embryo CAM model for inhibition of induced angiogenesis, whereby induction is achieved with soluble compounds, like bFGF and/or VEGF, or with tumor and transformed cell line implants,
- differentiation of integrin usage-($\alpha_v\beta_3$ versus or $\alpha_v\beta_5$ or else) in angiogenesis in response to different stimuli and in conjunction with determination of integrin selectivity of the inhibitors,

Provision of in vivo testing capacity for more than 10 compounds selected by EMD for

- use as inhibitors in SCID mouse/human skin chimera to inhibit angiogenesis and/or take of skin transplant, and/ or use of this model with intradermal tumor to inhibit angiogenesis and/or tumor development,

Dr. Martin Friedlander:

Consultancy for EMD to determine in vivo the function and activity of the compounds used,

development and use of angiogenesis models in rabbit to test the integrin inhibitors,

testing of EMD-derived and/or TSPI-derived integrin inhibitors selected by EMD,

Provision of in vivo capacity of 10 compounds per year selected by EMD for

use as integrin inhibitors is rabbit eye models to inhibit angiogenesis, whereby angiogenesis is induced by soluble factors like bFGF and/or VEGF, or by tumor or transformed cell line implants,

use as integrin inhibitors in rabbit VX2-carcinoma model to inhibit tumor angiogenesis and development.

Dr. K.C. Nicolaou:

Design and synthesis of non-peptidic chemical entities for αv and/or β3- integrin inhibition exclusively for Merck/TSRI - cooperation,

synthetic capacity of 3 post-doctoral fellows per year,

supply of sufficient amounts of synthetic compounds to laboratories of Dr. Cheresh and at Merck for in vitro testing,

supply of sufficient amounts of synthetic compounds selected by Merck to laboratories of Dr. Cherish and Dr. Friedlander, and at Merck on demand for in vivo testing.

Obligations of Merck in cooperation with TSRI:

Merck will test compounds of EMD- and/or TSRI-origin in vitro in isolated integrin binding studies and integrin mediated cell adhesion studies, as well as in in vivo models.

Toxicological, pharmacokinetic and biodistribution studies will be initiated by Merck.

Clinical studies will be under the auspices of Merck.

Preclinical Research Merck KGaA

By: _____
Dr. Jan Sombroek
Head Preclinical R&D

Composite (Year 1)

Investigator	CHERESH	FRIEDLANDER	NICOLAOU	TOTAL
Personnel	$ 238,000	$ 124,355	$ 92,820,	$ 455,175
Supplies	63,000	42,952	64,000	169,952
Animals	142,175	39,600	0	181,775
Direct Costs (less equipment)	443,175	206,907	156,820	806,902
Overhead @ 70%	310,223	144,835	109,774	564,832
Subtotal	753,398	351,742	266,594	1,371,734
Equipment	100,000	250,000	0	350,000
Total Direct & Overhead	853,398	601,742	266,594	1,721,734
ISR @ 25%	213,350	150,436	66,649	430,435
Total Cost Year 1	1,066,748	725,178	333,243	2,152,169
Year 2	979,416	457,264	346,573	1,783,253
Year 3	1,018,595	475,550	360,433	1,854,578
Total	$ 3,064,759	$ 1,684,992	$ 1,040,249	$ 5,790,000

(1) Annual amounts to be paid in equal quarterly payments in advance to Scripps

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APPENDIX 12 — DRAFT OF RESEARCH PROPOSAL SUBMITTED BY DR. CHERESH TO MERCK ATTACHED TO THE 1995 AGREEMENT (FEBRUARY 1995 DRAFT)

Scripps/E. Merck Program on
Angiogenesis

Submitted February 1, 1995

Scripps/E. Merck Program on Angiogenesis

Principal Investigator: David A. Cheresh, Ph.D.

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Introduction

-Angiogenesis in cancer and human disease
-Tumors induced angiogenesis
-Angiogenesis in eye disease
-Angiogenesis in inflammation
-Mechanisms of angiogenesis
-The search for angiogenesis inhibitors
-Role of the integrin $\alpha_v\beta_3$ in angiogenesis

Goals and specific aims

-Overall goal:
-Specific Aims 1-5

Current in vivo Angiogenesis Models at TSRI

-Chick CAM
-Mouse/human chimeric model
-Rabbit cornea

Animal Models Under Development

-Rabbit VX2 carcinoma
-Spontaneous cancer in dogs
-Arthritis in rabbits
-Restenosis in rabbits
-Primate stroke

Role of Scripps Investigators in Program

Collaboration Between Scripps and E. Merck

Time Scale for Propose Studies

References

Letters From Collaborators at TSRI
K.C. Nicolaou, Ph.D.
M. Friedlander, M.D., Ph.D.
Beth Ford, D.V.M., (TSRI, Director of Animal Facilities)
Thomas Fitting, J.D., Ph.D. (TSRI, Patent Attorney)

Tentative Budget

* * *

[Commencing at page 9]

[9] all primary and some transformed cells (Meredith, J., et al, 1993; Montgomery, A., et al, 1994). Inhibition of angiogenesis by LM609 or a cyclic peptide antagonist of VNR leads to tumor shrinkage and complete necrosis by eliminating the nutrient supply (Brooks, P., et al, 1994b). LM609 also inhibits new blood vessel growth in the rabbit corneal pocket eye angiogenesis model, a choroidal angiogenesis model and an iris intraocular melanoma model (Friedlander, M., et al, in preparation). By binding only to sites of neovascularization *in vivo*, LM609 and cyclic peptide antagonists of VNR are excellent drug candidates for anti-angiogenic therapies.

GOALS AND SPECIFIC AIMS

[10] **Overall Goal:** To develop specific angiogenesis inhibitors based on antagonists of vascular cell integrin function for the treatment of human diseases.

Specific Aims:

1) To expand the use of currently available models of cancer-induced and ocular angiogenesis and to develop additional models of cancer-induced angiogenesis such as the rabbit VX2 carcinoma. These models are designed with the intention to examine the efficacy of E. Merck and TSRI-derived angiogenesis inhibitors. These models are in operation and have been fully approved by our animal rights committee. Integrin antagonists will be tested for efficacy, pharmacokinetics, biodistribution and toxicity in these models.

2) To extend our collaboration with Dr. K.C. Nicolaou, Chairman of the Chemistry Dept at TSRI, who has already designed specific non-peptide mimetic antagonists of integrin $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$. These compounds will be examined in purified receptor assays, cell adhesion assays and angiogenesis models in vivo. Based on results obtained in these models, the chemical structures of these compounds will be modified to obtain the most potent, specific, non-toxic inhibitors of angiogenesis in vivo.

3) To examine the molecular role of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ in angiogenesis in response to specific cytokines such as bFGF, VEGF, TNFα, and TGFα. This will involve both in vivo and

in vitro analysis of vascular cell biological activity. We will examine the role of integrin antagonists on vascular cell signal transduction, invasion, proliferation, differentiation and apoptosis.

4) To examine a wide variety of human tumor tissue for the expression of [11] angiogenic cytokines and integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. This information will establish whether certain types of cancer might be more susceptible to blockage of angiogenesis with antagonists of $\alpha_v\beta_3$ or $\alpha_v\beta_5$.

5) To explore other disease models in which angiogenesis and $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin antagonists may play an important role. This will include an analysis of cytokine and integrin expression in vascular diseases such as in carotid plaques and restenotic vessels as well as in inflammatory tissues such as rheumatoid arthritis, and psoriasis. We will examine the effect of integrin antagonists in a rabbit model of arthritis as well as in rabbit and porcine models of restenosis. We will also extend our collaboration with Dr. Greg del Zoppo to explore the role of $\alpha_v\beta_3$ in primate models of stroke since previous studies have shown this integrin becomes expressed within hours of experimental ischemic injury in the brain.

CURRENT IN VIVO MODELS AT SCRIPPS

1) **Chick CAM embryo model.** To investigate angiogenesis in response to recombinant cytokines and human tumor fragments. This model will be used to assess the role of angiogenesis inhibitors on primary tumor growth and spontaneous pulmonary and hepatic metastasis of human tumors. Also, this model will allow us to examine whether

individual cytokines potentiate angiogenesis via distinct integrins such as $\alpha_v\beta_3$ and $\alpha_v\beta_5$.

Advantages: Allows for the rapid examination of angiogenesis in three days or tumor growth and metastasis in seven days. Also, this model is relatively inexpensive and may be useful as an initial screen to assess the relative potency of inhibitors. This model does not require separate animal facilities. Allows for the isolation of vascular cells directly from the CAM for biochemical and biological [12] analysis, in vitro as previously described by Brooks et al. Cell, 1994. Monoclonal and peptide antagonists of human integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ recognize these receptors in the chick. Allows for topical or systemic testing of inhibitory compounds.

2) **Mouse/human chimeric model.** This model utilizes SCID mice transplanted with full thickness human skin. This model will be used to examine human tumor growth and the role of angiogenesis in this process. This model depends on the growth of human blood vessels in the transplanted skin. In addition, we will examine the role of recombinant cytokines to stimulate human vascular growth and the role of integrins in this process.

Advantages: This models allows one to examine human angiogenesis in human tissue in response to a human tumor or recombinant cytokines. This model allows for immunohistochemical analysis of human blood vessels during their invasion into human tumors and should allow the identification of relevant adhesive ligands involved in angiogenesis of human tumors. This model will also enable an assessment of the specific cytokines involved in various

human tumor-induced angiogenesis. It will also enable an examination of the involvement of particular integrins in angiogenesis stimulated by specific recombinant cytokines.

3) **Rabbit cornea.** This model is classically used by investigators for the development of angiogenesis antagonists as possible therapeutics. This model will be used to examine angiogenesis induced by distinct cytokines, such as bFGF, VEGF and TNFα or tumors as well as the effectiveness of integrin antagonists in preventing this process.

Advantages: This model is a classic preclinical model that has been used by a wide number of investigators to test the therapeutic index of anti-angiogenic compounds. It is easy to monitor and we have established a method for precise quantification of [13] angiogenesis. This model has relevance for ocular angiogenesis. A control and experimental compound can be examined simultaneously in the same animal (left and right eye, respectively). This model can also serve to test topical, intraocular and intravascular routes of treatment. Antibodies and peptides antagonists to human integrins react well with the rabbit.

ANIMAL MODELS UNDER DEVELOPMENT AT TSRI

1) **Rabbit VX2 carcinoma.** This is an experimental model of tumorigenicity and metastasis in which a rabbit carcinoma cell line (VX2) is transplanted subcutaneously into the same species of rabbit from which the cell line was derived. Within two weeks, palpable tumors are formed. This model has been used previously to evaluate the effects of anti-tumor agents. Tumor dimensions before and after administration of anti-αv

integrin and control reagents by an intravenous or other route will be determined. After treatment, tumors will be surgically removed and weights determined. Histological analysis of treated tumors will be performed.

Advantages: This is a reproducible model of tumorigenicity and metastasis in a mammalian species with demonstrated cross-reactivity of anti-αv integrin reagents. It also utilizes the same species that will be used for pharmacokinetics, biodistribution and toxicology studies and will permit optimization of angiogenesis antagonism strategies. Useful for evaluation of efficacy of anti-$\alpha_v\beta_3$ reagents as well as for treatment regimen determination.

2) **Spontaneous cancer** in dogs (melanoma, breast, osteosarcoma) and cats (breast). Animals with tumors will be treated with anti-αv integrin and control reagents. Tumor size will be evaluated before and after treatment by ultrasound imaging [14] techniques.

Advantages: Dog and cat αv integrins cross-react with anti-αv integrin reagents. Spontaneous tumors in animals are the closest representatives to human spontaneous tumor disease. These studies in larger mammalian species will be useful for further determination of treatment regimens that may be appropriate in humans.

3) **Antigen or adjuvant induced arthritis in rabbits.** Injection of lipopolysaccharide, albumin in complete Freund's adjuvant or cytokines (e.g., IL-8, TNFa) into the knee joint of rabbits induces arthritic symptoms which include swelling, angiogenesis and edema within 7-14 days.

After administration of anti-αv integrin and control reagents, joint size and temperature will be evaluated followed by histological analysis for number of blood vessels and lymphocytes per unit area as well as extent of cartilage and bone degradation.

Advantages: This is a rapid, inducible model of arthritis in a species with demonstrated cross-reactivity of anti-αv integrin reagents. This model will permit evaluation of these anti-angiogenic reagents for their efficacy in ameliorating the symptoms of arthritis.

4) **Restenosis in rabbits, swine.** Neointimal hyperplasia is induced by injuring the arterial vessel wall with a balloon catheter (mimicking balloon angioplasty). Maximum smooth muscle cell proliferation and lumen occlusion occurs within seven to fourteen days. After administration of anti-αv integrin and control reagents, lumen size will be determined.

Advantages: These are rapid, inducible models of human restenosis in two species which have demonstrated reactivity with anti-αv reagents. Preclinical and clinical data from Centocor's ReoPro (a chimeric anti-β3 Fab which is now approved by the [15] FDA for high risk percutaneous transluminal coronary angioplasty) suggests that a β3 integrin, likely $\alpha_v\beta_3$, plays a significant role in restenosis.

5) **Primate (Baboon) stroke model** with Dr. Del Zoppo at TSRI. This is based on our knowledge that integrin $\alpha_v\beta_3$ levels increase within 12 hours after ischemic injury of the middle cerebral artery. In addition, we showed that all blood vessels that showed $\alpha_v\beta_3$ expression after ischemic injury had

fibrinogen and platelets. These findings suggest the possibility that $\alpha_v\beta_3$ on the vascular cell surface may promote fibrinogen binding leading to the deposition of platelets. This in turn would enhance the degree of ischemic injury after stroke.

ROLE OF SCRIPPS INVESTIGATORS

The Scripps Research Institute will initiate an in depth angiogenic program to investigate the role of integrin antagonists on diseases associated with angiogenesis such as solid tumor growth and metastasis, adult blindness, inflammatory disease, stroke and neointimal thickening after angioplasty. The structure of this program will involve a scale-up and extension of the long standing collaborative funding arrangement with the Cheresh laboratory. However, we plan to utilize the strengths of TSRI and to involve two other groups, headed by Martin Friedlander, M.D., Ph.D. and K.C. Nicolaou, Ph.D. (see letters of collaboration). In addition we will work closely with Beth Ford D.M.V. who heads the TSRI animal facilities (see letter of collaboration). She will assist us with all phases of these studies including the arrangement of canine spontaneous tumors.

The benefits of this TSRI program are several fold. First, we have in place various in vitro and in vivo models to evaluate the specificity, efficacy and toxicity of integrin antagonists as potential anti-angiogenesis drugs. The Cheresh laboratory is widely recognized as a leader in integrin biology as well as angiogenesis. Second, [16] we believe our patent is quite strong and will be issued by 1997 (see letter from our patent attorney, Thomas Fitting). Third, Dr. Friedlander

provides expertise in receptor cell biology and biochemistry, as well as angiogenesis and neovascular eye disease. He is a qualified ophthalmologist with clinical specialty training in vitreoretinal diseases and a clinical practice largely devoted to proliferative vascular eye disorders such as diabetes and macular degeneration. Fourth, we will collaborate closely with Dr. K.C. Nicolaou, who has already begun to design and synthesize, non-peptide integrin antagonists for analysis in our models. Dr. Nicolaou is among the most respected and capable synthetic organic chemists in the world. He recently reported the complete synthesis of Taxol. Fifth, novel basic research discoveries and chemical compound discovered under this agreement may provide additional exciting new drug leads for diseases characterized by angiogenesis. Finally, this program is an extension of our previously highly successful agreement between Scripps and E. Merck.

COLLABORATION BETWEEN SCRIPPS AND E. MERCK:

The goal of this program will be to take advantage of the strengths of E. Merck and Scripps to best develop integrin antagonists as angiogenesis inhibitors. Thus, compounds designed and synthesized at E. Merck will be directly tested at Scripps. For example, we will test for integrin binding in vitro and then assess each compound in a series of animal models. We will utilize the chick CAM, SCID mouse and rabbit corneal model initially. We will examine each compound for half-life, toxicity and efficacy. We will send E. Merck samples of blood taken from animals at various times post-injection which will then be subjected to quantitative and qualitative analysis.

We will employ a highly trained laboratory manager who will prepare monthly progress reports outlining the progress our studies. We will make at least [17] two trips per year to E. Merck to discuss the studies in depth and to decide how best to proceed. All new discoveries will be disclosed through our technology transfer office for potential licensing by E. Merck as has been done in the past. We would welcome E. Merck scientists to visit our facilities and assist in the technical and conceptual design of this program.

E. Merck is in position to scale-up the production and purification of any lead compounds developed here. This will allow further testing and analysis in our models for any compounds that show promise.

TIME SCALE FOR PROPOSED STUDIES:

We propose a three year time frame to develop this program. It is anticipated that within the third year clinical trials will begin and patent approval will be granted.

Year 1: We will initiate additional models and begin testing the E.M. peptide 66203 and Mab LM609 for efficacy. Pharmacokinetics and toxicity testing will be initiated in rabbits. We will test the role of $\alpha_v\beta_5$ antagonist Mab P1F6 in VEGF verses bFGF-induced angiogenesis. Tumor biopsies and normal tissues will be examined by immunohistochemical for presence of $\alpha_v\beta_3$, $\alpha_v\beta_5$ and various angiogenic cytokines, such as VEGF, bFGF, TNF and TGFα. Petidometics produced in K.C. Nicolaou's laboratory will be tested in cell adhesion experiments, to determine rank order potency toward $\alpha_v\beta_3$ or $\alpha_v\beta_5$. This will also be performed

for all E. Merck derived compounds. Each structure will be assessed with peptide and antibody controls, in in vivo models of angiogenesis, chick CAM, SCID mouse and rabbit eye.

Year 2: Studies from year 1 will continue. All in vivo models will be fully operational. We will begin testing second, third and fourth generation peptides and [18] mimetics for efficacy, safety and Pharmacokinetics. Based on evidence obtained in year 1, clinical contacts for specific cancer indications will be developed. Also, under the direction of Dr. Friedlander, ocular trials will be planned. We anticipate that compounds previously optimized for potency will require chemical modifications to increase half-life. These will then be tested in all relevant models. Biochemical studies will be performed to characterize vascular cell signaling via integrins $\alpha_v\beta_3$ verses $\alpha_v\beta_5$. Antagonists developed above will be tested for their impact on these signaling events.

Year 3: Based on toxicological data an IND will be filed together with clinical collaborators for cancer as well as eye disease. Any additional data required at that time will be gathered to satisfy the F.D.A. Patent approval will likely depend on our ability to support claims regarding mimetics. Thus, lead compounds will be used to generate data required by the patent examiner deemed necessary for patent approval. Clinical trials (phase I/II) for specific cancer indications and macular degeneration will begin.

APPENDIX 13 — UNIFORM CONSULTING AGREEMENT BETWEEN DR. CHERESH OF SCRIPPS AND DR. SOMBROEK OF MERCK, DATED OCTOBER 6, 1995

THE SCRIPPS RESEARCH INSTITUTE UNIFORM CONSULTING AGREEMENT PROVISIONS

1. All arrangements and agreements in which a member of the staff of The Scripps Research Institute ("TSRI") provides consulting services to any profit making or commercial organization (hereinafter referred to as a "Company") shall refer to these Uniform Consulting Agreement Provisions ("Uniform Provisions") by specific reference and attach same to the agreement or include same verbatim in the agreement. If anything in an agreement to provide consulting services between Company and a TSRI staff member (Consultant) is inconsistent with these Uniform Provisions, these Uniform Provisions shall govern. No such agreement shall be of any force or effect unless it is subject to these Uniform Provisions and is approved in writing by TSRI's Office of Technology Transfer.

2. TSRI staff members shall spend no more than a total of ten percent of their professional effort in consulting services for all Companies. Consulting agreements shall specify the amount of time to be expended in consulting for the Company. Consulting fees shall be paid directly to the Consultant. Such consulting services shall not involve any research or laboratory work.

3. Neither the name nor reputation of TSRI, Scripps Institutions for Medicine and Science ("SIMS"), or Scripps

Health ("SH") shall be publicized or exploited directly or indirectly by the Company. The Company and the Consultant shall hold TSRI, SIMS and SH and their officers, trustees, and employees harmless from all claims, charges damages, and judgments arising from consulting services and shall indemnify TSRI, SIMS and SH for costs, direct and indirect, of defending any action arising from the consulting agreement or services performed thereunder. Neither the Company nor the Consultant shall use any services, personnel, facilities or equipment of TSRI in performing consulting services.

4. Consultant's rights, title and interest in inventions, discoveries and developments arising from Company funded consulting services made solely or jointly with Company employees or agents may be assigned to the Company, so long as the provisions in Section 5 below are not applicable.

5. Company shall not obtain any rights in or respecting any invention, discovery or development of the Consultant which: (a) was conceived, reduced to practice, published, or submitted for publication, by the Consultant before the effective date of the consulting agreement, (b) was at any time conceived or reduced to practice independent of consulting services performed hereunder, (c) is the result of work conducted within TSRI, (d) is subject to Consultant's obligation to assign to TSRI, and/or (e) relates in any manner to the business of TSRI.

6. The Company shall have no rights or interests in any of the inventions, discoveries, developments, improvements, or products which may arise from the research or other scientific work performed by the Consultant outside the scope of the

consulting agreement or performed by other scientists of TSRI. Further, it is understood that the Consultant shall not disclose to the Company any such research or other scientific work to the extent that any such disclosure might impair the patent rights or the proprietary rights of TSRI or other third parties.

7. In the event of any dispute as to whether TSRI has any rights in an invention which Company claims to own, the determination of inventorship, conception, and/or reduction to practice shall be determined jointly by patent counsel for TSRI and patent counsel for Company, according to the patent laws of the United States. In the event such patent counsel cannot mutually agree, then the determination shall be by a independent patent lawyer to serve as the arbitrator. TSRI and Company shall share equally in paying the costs and fees of the independent patent attorney. The arbitrator may interview all persons and review all documents which the arbitrator deems necessary or proper to reach a determination. Such determination shall be binding upon TSRI and Company, excepting only, however, if a different determination is made later by the United States Patent and Trademark Office or by a United States court in proceedings initiated by a third party (other than TSRI or Company), and TSRI and Company are given an opportunity to participate in said proceedings, then TSRI and Company hereby agree to be bound by said different determination.

8. Nothing in the consulting agreement shall limit or be construed to limit the right of Consultant or of TSRI to use or publish information which (a) was in the public domain before the consulting services were performed, (b) was

known to Consultant or TSRI, respectively, before the consulting services were performed, (c) was developed or acquired independently of the Company or TSRI, or (d) becomes public knowledge without breach by Consultant of any obligations of confidence to Company or TSRI.

8. Nothing in the consulting agreement shall limit or be construed to limit the right of Consultant or of TSRI to use or publish information which (a) was in the public domain before the consulting services were performed, (b) was known to Consultant or TSRI, respectively, before the consulting services were performed, (c) was developed or acquired independently of the Company or TSRI, or (d) becomes public knowledge without breach by Consultant of any obligations of confidence to Company or TSRI.

9. The Uniform Provisions shall be and hereby are in force and effect for the entire term of any consulting agreement between Consultant and Company.

10. Upon termination of consulting services, the Consultant shall, if requested by the Company, leave all notes and records of his/her consulting services with Company, shall be entitled to retain one copy thereof for archival purposes, subject to any obligations of confidence to Company.

11. If the Company calls upon the Consultant to testify in any expert capacity, in Court, deposition or otherwise, the Company shall pay the Consultant for all time spent in preparing for and giving such testimony at a rate no lower than a pro rata fee commensurate with the consulting fee set forth in the consulting agreement, adjusted for inflation, and

in addition, shall pay lodging, travel and other actual costs incurred by the Consultant in connection with such testimony.

12. The consulting agreement and these Uniform Provisions shall be construed and enforced in accordance with the laws of the State of California and the United States patent laws.

ACCEPTED:

Company By: s/ [illegible]
Date: [illegible]

Title: Head of Preclinical

ACCEPTED:

Consultant: s/ [illegible] Date: 10/6/95

Contract approved for The Scripps Research Institute, La Jolla, California, this 6th day of October, 1995.

s/ Jennifer Dyer
Jennifer Dyer
Senior Technology Transfer Officer
The Scripps Research Institute

APPENDIX 14 — LETTER FROM DR. CHERESH TO DR. RADUNZ OF MERCK REPORTING TUMOR SHRINKAGE USING EMD-6, DATED MAY 4, 1994

THE SCRIPPS RESEARCH INSTITUTE
10666 North Torrey Pines Road
La Jolla, California 92037
619 455-9100

May 4, 1994

Hans-Eckart Radunz, Ph.D.
E. Merck
Postfach 41 19
6100 Darmstadt 1
Frankfurter, Strabe 250
Germany

Dear Hans:

I hope all is well. Please find enclosed the results of our I.V. peptide tumor experiment. We have now shown that we can cause the shrinkage of 40mg tumors with 66203 after 7 days. A 40mg tumor fragment derived from a human lung adenocarcinoma was placed on a 10 day old chick CAM. After 24 hours the embryos were inoculated I.V. with 300ug of peptide. Tumors were allowed to grow for 6 more days and then resected and weighed. As you can see #66203 produced a four fold reduction in tumor weight. Histological examination revealed that no viable tumor cells could be found in the embryos treated with #66203.

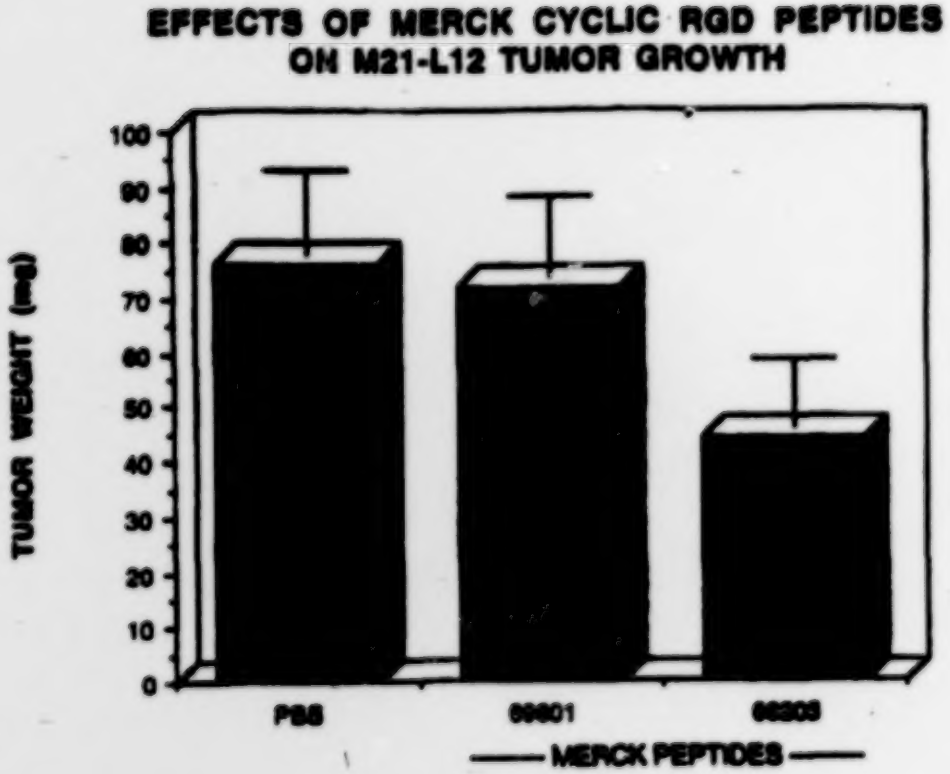
These results are most promising and complement those results I sent you on tumors examined after 3 days. We are now writing up these data. However, as usual we need additional peptide, 50mgs of any active and control peptides to complete these studies.

I will send you a copy of our manuscript as soon as it is written. I wish you and your colleagues all the best.

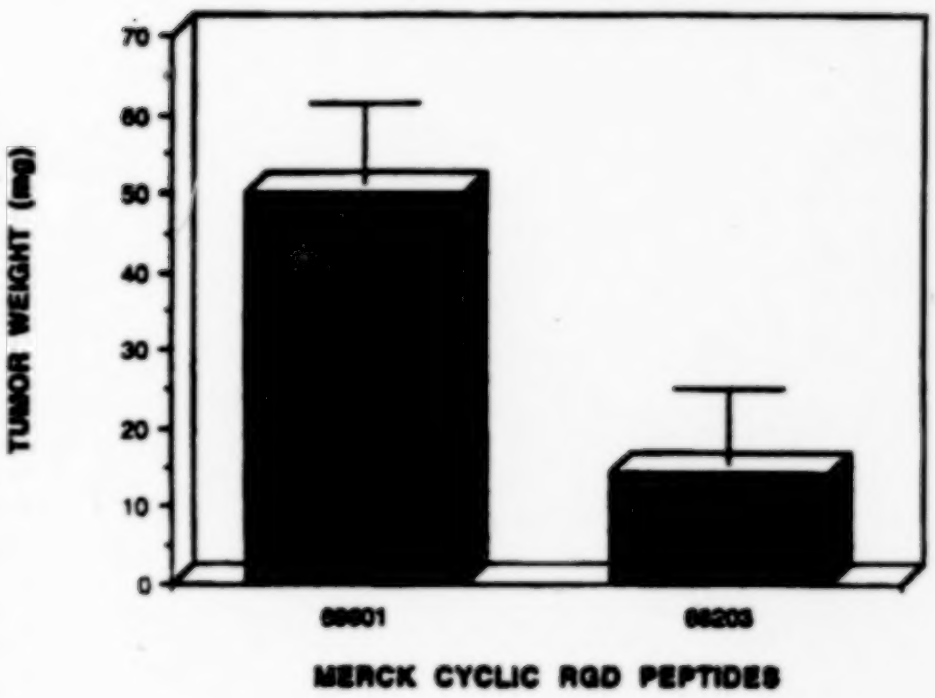
Sincerely,

s/ David
David A. Cheresh, Ph.D.

David A. Cheresh, Ph.D.
Tenured Associate Member, Department of Immunology.
Direct Line: 619 554-8281
Fax Line: 619 554-6705.



EFFECTS OF MERCK CYCLIC RGD PEPTIDES ON UCLAP3 TUMOR GROWTH



APPENDIX 15 — LETTER FROM DR. CHERESH TO DR. RADUNZ OF MERCK DISCUSSING RENEWAL OF COLLABORATION, DATED JUNE 24, 1994

THE SCRIPPS RESEARCH INSTITUTE
10666 North Torrey Pines Road
La Jolla, California 92037
619 455-9100

June 24, 1994

Dr. Hans-Eckart Radunz
E. Merck
Postfach 41 19
6100 Darmstadt 1
Frankfurter, Strabe 250
Germany

Dear Hans:

I hope all is well with you and your colleagues. Things are progressing quite well in the angiogenesis project. Peter Brooks and myself are completing two papers which document the ability of $\alpha_v\beta_3$ antagonists to block the growth and metastatic (spontaneous) of various human tumors. These papers will be sent to you shortly. We have also now developed a chimeric nude mouse containing a surgically implanted piece of human skin. Therefore, we are now measuring human angiogenesis toward human tumors in a human tissue *in vivo*. Also, we are collecting serum from the chick embryos treated with EM66203 to send Dr. Jonczyk for half-life studies.

We are interested in testing the peptide in Dr. Del Zoppo's Baboon stroke model. We are currently writing our manuscript describing the expressing of $\alpha_v\beta_3$ on brain blood vessels following ischemic injury. This manuscript will also be forwarded to you soon.

As you may be aware, July 1994 begins the last year of our collaborative agreement. When we last spoke you indicated as interest in continuing this interaction. I believe this to be of particular benefit due to our recent findings on angiogenesis. At this time E. Merck is in a good position to develop peptide based antagonists of angiogenesis for treatment of cancer and inflammatory diseases. Based on our original agreement E. Merck should state its interest in continuing this collaboration as soon as possible since our agreement is scheduled to end July 1995.

I look forward to hearing from you soon. Take care.

Sincerely,

s/ David

David A. Cheresh, Ph.D.
Tenured Associate Member, Department of Immunology
Direct Line: 619 554-8281 Fax Line: 619 554-6705

APPENDIX 16 — LETTER FROM DR. CHERESH TO DR. JONCZYK OF MERCK PROPOSING TERMS OF NEW COLLABORATION, DATED DECEMBER 22, 1994

THE SCRIPPS RESEARCH INSTITUTE
10666 North Torrey Pines Road
La Jolla, California 92037
619 455-9100

December 22, 1994

Dr. Alfred Jonczyk
E. Merck
Postfach 41 19
6100 Darmstadt 1
Frankfurter StraBe 250
Germany

Dear Alfred,

Thank you for your recent letters of December, 20 and December 2. I have not answered your original letter since I have been giving considerable thought to the proposal. In talking with my associates at Scripps I have come up with proposal that might best move this project forward.

One option for your consideration involves a sizable increase in the support of this project at Scripps over two years that would then serve as the basis for potential clinical trials to begin at Scripps and perhaps at other institutions in the second and third year.

The goal of the first year would be to scale up our animal experiments including the chick embryo, SCID mouse/human

chimera and with Dr. Martin Friedlander, the rabbit eye model. We would also propose to examine models involving angiogenesis during inflammation. This would involve hiring several scientists and at least one clinical scientist as well as several specialized technicians. I am confident that, if this program is acceptable to E. Merck, Scripps would make available the necessary lab space and animal facilities to accomplish this work. This would be the most rapid way to push this project since these models are currently in operation here at Scripps. If we were to set up some separate company, foundation, or other organizatio n, it would likely take several months to establish animal facilities and have appropriate paper work and regulatory approval in place to begin our studies.

Therefore, the funding would continue and extend the E. Merck supported angiogenesis program here at Scripps. Utilizing facilities in place here provides a tremendous advantage. In addition, this would help in gaining an international recognition for this work. I propose these studies be performed with Dr. Friedlander, as he has established the rabbit eye model and is an eye surgeon with extensive scientific training. I think it would be extremely beneficial for Dr. Friedlander and myself to visit you in the near future to review our plans, and obtain your thoughts. By keeping this associated with Scripps we can best take advantage of the excellent collaboration with E. Merck that has been in place since 1988.

In general terms, I would propose initial start-up funds of approximately $1,500,000 direct cost ($U.S.) to cover equipment, personnel, supplies, and animals. A portion of

these funds, approximately $400,000 would directly support Dr. Friedlander's work. This level of support would be extended for one additional year to allow us to complete any preclinical model testing required for clinical trials. In the third year we would propose to extend and increase the funding to include clinical trials in a cancer related and ocular related disease. I have several excellent clinical contacts for cancer and Dr. Friedlander is well connected with the key opthamologists in the U.S. The funding level of the third year would clearly depend on milestones achieved in year one and two and the type of clinical trial initiated. Of course, we will soon provide a detailed budget for years one and two. Also, I propose we discuss these plans in detail with you and your colleagues to best design the program to meet all needs and concerns.

If possible, I would like to propose your consideration of a collaboration with Ixsys, the biotech company that is developing the humanized LM609. I believe this may be the first actual $\alpha_v\beta_3$ antagonist to find its way into the clinic. However, I believe E. Merck has a tremendous interest in the outcome of this approach as it would serve as "proof of principle" facilitating the peptide or mimetic program. Perhaps the best way to include Ixsys in a collaborative arrangement would be for E. Merck to first make a commitment to this program at Scripps, and then approach Ixsys with a collaborative opportunity that could be beneficial to all parties concerned.

The overall goals of our Scripps/E. Merck collaboration would be not only to test the E. Merck compounds in the angiogenic models, but to further develop the science relating

to angiogenesis. We have several new ideas under development in the laboratory that I believe may offer novel ways to block angiogenesis. These could be further developed and exploited appropriately with such funding.

Once I hear back from you regarding the general interest in this approach I will provide a detailed proposal with a budget outlining the goals of our studies. As I mentioned this must include some funding for the development of basic research since that is precisely the kind of work that lead to our discoveries on angiogenesis. By supporting the basic and applied aspects of angiogenesis in this manner, I can attract the best scientists and technical people to push this project forward. This will serve our mutual interests in developing $\alpha_v\beta_3$ antagonists as inhibitors of angiogenesis in human disease.

I look forward to your reply. Also if you and your colleagues have any ideas on ways to facilitate this I am open to ideas.

A final note, could you please provide us with the structure of E. Merck peptide #69601. Also, if you have any non-RGD peptide, or non-peptide antagonists of $\alpha_v\beta_3$ that we could test in our angiogenesis assays, let me know as soon as possible. This would greatly strengthen the claims of our angiogenesis patent application, thereby allowing the broad claims of perhaps all $\alpha_v\beta_3$ antagonists. I am convinced that once our Cell paper comes out other companies will attempt to patent their non-RGD or nonpeptide $\alpha_v\beta_3$ antagonists for angiogenesis. Therefore, we must strengthen claim #1 in our patent application as soon as possible. This will clearly strengthen the value of the E. Merck license of this patent.

I wish you a fine holiday season and a happy New Year.

Sincerely,

s/ David
David A. Cheresh, Ph.D.
The Scripps Research Institute
Depts. of Immunology and Vascular Biology

DAC/trg

APPENDIX 17 — FAX LETTER FROM DR. SOMBROEK OF MERCK TO DR. CHERESH, DATED FEBRUARY 20, 1995

MERCK

TELEFAX

To: *Mr. David A. Cheresh, Ph.D.*
Telefax No.: *001 619 554 8926*
Company: *The Scripps Research Institute*
Department: *Departments of Immunology & Vascular Biology*

Scripps/E. Merck Program on Angiogenesis

Dear Dr. Cheresh,

It is a pleasure for me to inform you that within the pharmaceutical division of E. Merck we have come to an agreement to sponsor the Program on Angiogenesis as described in your proposal "Scripps/E. Merck Program on Angiogenesis".

Dr. Luckenbach will be responsible for working out the necessary contractual arrangements. He will contact you within the next few days.

I am convinced that we have established a brilliant international team on this project. I sincerely hope that this new concept in tumor treatment will lead to effective therapeutics.

With best personal regards,

Dr. Jan Sombroek
(Dictated by Dr. Sombroek, but sent off in his absence)

s/ [illegible]

APPENDIX 18 — LETTER FROM DR. SOMBROEK OF MERCK TO DR. CHERESH OF SCRIPPS, DATED APRIL 13, 1995

Dr. David A. Cheresh
SCRIPPS Clinic and Research Foundation
Immunology, IMM 13
10666 North Torrey Pines Road
La Jolla, CA 92037, USA

Dear Dr. Cheresh,

Dr. Alfred Jonczyk and Dr. Volker Linden reported about the pleasant meeting with you, and your colleagues Mr. Arnold LaGuardia and Mr. Douglas A. Bingham in New York. I believe good progress was made towards the new contract and a fruitful extension of the collaboration.

Dr. Jonczyk promised you a summary of what Merck will be able to pay for preclinical studies and synthetic efforts at TSRI during the next three years. This collaboration is aimed to lead the project as close to clinics as possible, and during your visit in February in Darmstadt I felt this was our mutual understanding and interest. We believe this support should enable you, Dr. Friedlander and Dr. Nicolaou to pursue the work in the proposed manner.

	Year 1	Year 2	Year 3	total
Million US $ incl. all surcharges, IDC, ISR, consultancy	2,4	1,73	1,87	6,0

In order to stay in these financial limits it might be advised to redesign some details of the program.

As Dr. Jonczyk mentioned already in New York, you might consider the following: Merck will take care of toxicological studies once we have defined a product for the pipeline. Pharmacokinetica, pharmacodynamics and biodistribution studies will routinely be performed at our institute in Grafing, unless we ask you to help us because of capacity problems.

It will be important for us to exchange our knowledge with you, Dr. Friedlander and Dr. Nicolaou on a routine basis. We believe our drug design group could have great input into synthetic strategies at TSRI. As you know, my colleagues are already synthesising non-peptidic inhibitors, and joining of efforts could be advantageous. In addition, we would like any new compound synthesised at TSRI to be tested in our labs (receptor binding inhibition and cell attachment). So, newly prepared inhibitors immediately should be transferred to Darmstadt.

In the preclinical in vivo testing we would like you to concentrate on tumor anglogensis using CAM-models, rabbit eye and mouse/human skin chimera. If a rabbit tumor and spontaneous cancer data from dogs and cats are raised, it will be interesting, but we expect those data are not necessary for FDA-approval. We suggest to keep the topics of arthritis, psoriasis and restenosis in your research proposal, but please refrain at the moment from actively pursuing these models. As I understood, the stroke models of Dr. Gregg del Zoppo are not included in your budget outlines and research proposal.

With best personal regards

s/ Jan Sombroek

Dr. Jan Sombroek
Head Preclinical R&D

cc: Dr. Lues, Dr. Raddatz, Dr. Matzku, Dr. Luckenbach, Dr. Jonczyk, Dr. Linden, Prof. Schnurr

APPENDIX 19 — MINUTES OF FIRST MEETING OF MERCK'S CORE TEAM FOR DEVELOPMENT OF EMD-8 ON NOVEMBER 26, 1996

MERCK

Participants:

Dr. Finke	cc:	Dr. Diekmann	Dr. Neirinckx
Dr. Jonczyk		Dr. Disselhoff	Dr. Raddatz
Dr. Rohmann		Dr. Hakert	Dr. Scheuble
		Dr. Hanstein	Prof. Schnurr
		Dr. Hintze	Dr. Seubert
		Dr. Hubl	Dr. Sombroek
		Prof. Leopold	Dr. Wiemann
		Dr. Lues	Dr. von Wietersheim

Minutes of the 1st Core Team Meeting EMD 85 189 (Zyklopeptid / Antiangiogenese) on November 26th, 1996

Management Summary

The EMD 85 189 project was designated as a development project at the PPSC-meeting on November 15th, 1996. Nomination of EPG-members will be initiated immediately. Discussion and detailed planning of production in compliance with GMP regulations must be carried out immediately in order to ensure the commencement of subsequent activities within the time schedule.

Project Activities **MERCK**

Toxicology	Responsible	Date
Two-week tox study will be discussed and planned immediately.	Drs. Jonczyk, Noll, Rosener	Dec. 96
The further toxicology programme will be drawn up in first quarter of 1997.		

Pharmacology	Responsible	Date
All pharmacological data relevant to the project so far will be put into Lotus Notes project database.		
The further pharmacology programme (models relevant to clinical trials) will be discussed and planned with all the EPG-members involved in first quarter of 1997.		
Basically a summary is required containing all relevant pharmacological results available so far. Dr. Jonczyk will give a presentation on this subject.	Dr. Jonczyk	Jan. 97

MERCK

Production	Responsible	Date
The production in compliance with GMP regulations will be discussed and planned immediately.	Drs. Arnold, Jonczyk, Noll, Seubert	Dec. 96, if possible

Authority Meetings

We agreed to hold meetings with the authorities, (FDA, PEI) as soon as possible to discuss our concept.

Prerequisites for the meetings:-

1. Investigator's Brochure
2. Clinical Development Plan
3. Toxicological results (2 week Tox)
4. Concept for the meetings

These meetings have been provisionally scheduled for the 4th quarter of 1997.

First of all, it is necessary to schedule the action items for points 1 - 4 and to designate responsibilities.

MERCK

A draft will be prepared as a discussion paper for the next core team meeting.	Dr. Noll	Jan. 97
All EPG-members concerned will be involved in concept phase.		

Miscellaneous

Dr. Jonczyk will compile a list of publications to date concerning the anti-angiogenic substance EMD 85 189.

The nomination of EPG-members will be initiated (Dr. Noll).

The EPG- kick-off meeting will be scheduled for February 1997. The meeting will be planned with MF (Dr. Noll).

An information day is recommended for 1997 for all people involved or interested in the project.

Initiation of project database in Lotus Notes (Dr. Noll).

The micro-pump-system is considered to be of interest in general. The progress of the development should be followed. It is not yet possible to predict whether this system will be relevant for this project.

The minutes will be handed over to all EPG-members as soon as they have been nominated.

s/ G. Noll
Dr. Gabriele Noll

APPENDIX 20 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 6: EFFECTS OF EMD 66203 AND 85189 ON MURINE RETINAL VASCULOGENESIS"

MERCK

REPORT 6

Confidential

Title: EFFECTS OF EMD 66203 AND 85189 ON MURINE RETINAL VASCULOGENESIS

Author(s):
Report prepared by: Amanda S. Heron, Theradex®

Date: August 25, 1997

RCK

* * *

1.0 ABSTRACT

Angiogenesis underlies the majority of eye diseases that result in catastrophic loss of vision. Recent evidence has implicated the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in the angiogenic process. The effects of systemically administered cyclic peptides antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ were studied using the retinal angiogenesis in a murine model. The two antagonists tested, EMD 85189 and 66203, specifically blocked new blood vessel formation with no effect on established vessels. These results suggest that antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ may be effective in treating individuals with blinding eye diseases associated with angiogenesis.

* * * *

APPENDIX 21 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 2: COMPARISON OF ANTI-ANGIOGENIC EFFECTS OF EMD 85189 AND 121974 IN THE CHICK EMBRYO CHORIOALLANTOIC MEMBRANE (CAM) ANGIOGENESIS ASSAY"

MERCK Angiogenesis Inhibition Studies in the Chick Embryo Chorioallautoic Membrane (CAM) Assay

EMD 69601, 85189, 121974

REPORT 2

Confidential

Title: COMPARISON OF ANTIANGIOGENIC EFFECTS OF EMD 85189 AND 121974 IN THE CHICK EMBRYO CHORIOALLANTOIC MEMBRANE (CAM) ANGIOGENESIS ASSAY

Author(s): Mauricio Rosenfeld, David A. Cheresh, Ph.D.
Report prepared by: Amanda S. Heron, Theradex®

Date: August 14,1997

* * *

1.0 ABSTRACT

The development of new blood vessels plays a critical role in a number of physiological and pathological events such as embryonal development, wound healing, arthritis and tumor growth and metastasis. Inhibition of angiogenesis reduces tumor perfusion and inhibits tumor growth. $\alpha_v\beta_3$ integrin receptors are found on the surface of activated (angiogenic) endothelial cells and are thought to be essential mediators of the early stages of angiogenesis. Agents binding to these receptors modulate adhesion between endothelial cells and a wide variety of extracellular matrix (ECM) components.

EMD 85189 and 121974 are $\alpha_v\beta_3$ and $\alpha_v\beta_5$ antagonists and were shown to inhibit the process of angiogenesis in several models. EMD 69601 is a negative control, very similar in structure to EMD 85189 and 121974. The anti-angiogenic effects of cyclic peptides EMD 85189 and 121974 were studied using the cytokine induced angiogenesis assay in chick CAM. Treatment with EMD 85189 or 121974 consistently resulted in inhibition of angiogenesis as compared to controls (PBS and EMD 69601). Importantly blocking angiogenesis in these models resulted in a dramatic regression of various human tumors.

Optimal dosing of the active peptides resulted in the complete inhibition of angiogenesis.

* * * *

APPENDIX 22 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 7: EFFECT OF ANGIOGENESIS INHIBITION BY ANTAGONISTS OF INTEGRIN $\alpha_v B_3$ IN A RABBIT MODEL OF RHEUMATOID ARTHRITIS"

MERCK Angiogenesis Inhibition Studies in a Rabbit Model of Rheumatoid Arthritis

EMD 66203, 69601, 85189

REPORT 7

Confidential

Title: THE EFFECT OF ANGIOGENESIS INHIBITION BY ANTAGONISTS OF INTEGRIN $\alpha_v\beta_3$ IN A RABBIT MODEL OF RHEUMATOID ARTHRITIS

Author(s):

Report prepared by: Amanda S. Heron, Theradex®

Date: October 14, 1997

* * *

1.0 ABSTRACT

Rheumatoid arthritis (RA) affects nearly three million Americans. Extensive investigation has failed to yield a conclusive etiology, and current therapies fail to stop the inflammatory progression which results in erosive joint destruction. Clearly, further modes of intervention in RA are necessary. In this respect, the extensive synovial neovascularization, which is a hallmark of RA, has been suggested to be an attractive target for therapy. However, our current understanding of angiogenesis is relatively limited and there are no effective drugs currently available to limit neovascularization in RA.

Angiogenesis is believed to be central to the pathophysiology of RA. Pathophysiologically, increased neovasculature translates into increased vascular bed volume which permits extravasation of blood-borne recruits into the synovial milieu. Increased neovasculature also results in increased endothelial mass which itself functions as a source of inflammatory cytokines and protease production. Further, the nutritional and metabolic requirements of the hyperproliferating synovium and invading pannus must be sustained. Thus, targeting of angiogenic endothelium in RA may represent a reasonable means of impacting many different aspects of this disease have been shown to inhibit angiogenesis.

$\alpha_v\beta_3$ integrin receptors are found on the surface of activated (angiogenic) endothelial calls and are thought to be essential mediators of the early stages of angiogenesis. EMD 66203 and 85189 are both RGD containing cyclic pentapeptide, non-tonic selective $\alpha_v\beta_3$ antagonists and proven inhibitors

of angiogenesis. These cyclic peptides were used to examine angiogenesis inhibition on early as well as established arthritis in a rabbit model of RA. EMD 66203 and 85189 $\alpha_v\beta_3$ antagonists were shown to impact the severity of arthritis when administered early in the course of disease.

* * * *

APPENDIX 23 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 5: EFFECTS OF INTEGRIN ANTAGONISTS CYCLIC PEPTIDES EMD 69601, 85189 AND 121974 AND MONOCLONAL ANTIBODIES LM609 AND P1F6, AS STUDIED IN THE RABBIT CORNEAL MICROPOCKET MODEL"

MERCK

Effects of Integrin Antagonists
Using the Rabbit
Corneal Micropocket Model

EMD 69601, 85189, 121974

REPORT 5

Confidential

Title: EFFECTS OF INTEGRIN ANTAGONISTS CYCLIC PEPTIDES EMD 69601, 85189 AND 121974 AND MONOCLONAL ANTIBODIES LM609 AND P1F6, AS STUDIED IN THE RABBIT CORNEAL MICROPOCKET MODEL

Author(s):

Report prepared by: Amanda S. Heron, Theradex®

Date: December 19,1997

* * *

1.0 ABSTRACT

Angiogenesis depends on cytokines and vascular cell adhesion events. Two cytokine-dependent pathways of angiogenesis were shown to exist and were defined by their dependency on distinct vascular cell integrins. In vivo angiogenesis in the rabbit micropocket corneal model induced by basic fibroblast growth factor (bFGF) depended on $\alpha_v\beta_3$, whereas angiogenesis initiated by vascular endothelial growth factor (VEGF) depended on $\alpha_v\beta_5$. Antibody to each integrin selectively blocked one of these pathways.

The effects of systematically administered cyclic peptide antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ on angiogenesis were also studied using the rabbit micropocket corneal model. These antagonists, EMD 85189 and 121974, specifically blocked new blood vessel formation with no effect on established vessels. These results reinforce the finding that antagonists of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ may be effective in treating individuals with blinding eye disease associated with angiogenesis.

* * * *

APPENDIX 24 — EXCERPT OF FDA REPORT PREPARED BY THERADEX, ENTITLED "REPORT 1: COMPARISON OF ANTITUMOR EFFECTS OF EMD 85189 AND 121974 IN A CHICK EMBRYO CHORIOALLANTOIC MEMBRANE (CAM) TUMOR GROWTH ASSAY"

MERCK
Chorioallantoic Membrane (CAM) Assay

EMD 69601, 85189, 121974

REPORT 1

Confidential

Title: COMPARISON OF ANTITUMOR EFFECTS OF EMD 85189 AND 121974 IN A CHICK EMBRYO CHORIOALLANTOIC MEMBRANE (CAM) TUMOR GROWTH ASSAY

Author(s):
Mauricio Rosenfeld, David A. Cheresh, Ph.D.
Report prepared by: Amanda S. Heron, Theradex®

Date: September 17,1997

* * *

1.0 ABSTRACT

The development of new blood vessels plays a critical role in a number of physiological and pathological events such as embryonal development, wound healing, arthritis and tumor growth and metastasis. Inhibition of angiogenesis reduces tumor perfusion and inhibits tumor growth. $\alpha_v\beta_3$ integrin receptors are found on the surface of activated endothelial cells and are thought to be essential mediators of early stages of angiogenesis. Agents binding to these receptors modulate adhesion between endothelial cells and a wide variety of extracellular matrix (ECM) components. Besides endothelial cells a variety of tissues, including certain tumors, can express the $\alpha_v\beta_3$ receptor. In order to avoid any direct effects on tumor cells, the tumor cell lines used in this study were selected for their lack of $\alpha_v\beta_3$ receptor expression.

EMD 85189 and 121974 are $\alpha_v\beta_3$ and $\alpha_v\beta_5$ antagonists and were shown to inhibit the process of angiogenesis in several models. EMD 69601 is not an $\alpha_v\beta_3$ antagonist, it was used as a negative control and did not inhibit tumor growth in any of the experiments. The anti-tumor effects of cyclic peptides EMD 85189 and 121974 were studied using the chicken chorioallantoic membrane (CAM) tumor growth assay. EMD 85189 was tested against a human melanoma cell line (M21-L), a human lung adenocarcinoma cell line (UCLAP3) and a human pancreatic carcinoma cell line (FgM). EMD 121974 was investigated in an experiment with the M21-L cell line.

Treatment with EMD 85189 resulted consistently in a complete inhibition of tumor growth as compared to controls. This effect appeared to be most prominent in the M21-L tumor cell line, where even tumor regression was observed. Treatment with EMD 121974 showed the similar effect as EMD 85189 with regard to the inhibition of M21-L growth, the only tumor line in which it was tested. Since M21-L tumor cells do not express the α_v integrin component, integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are not present on the tumor cell surface. Therefore, the tumor regressions caused by antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are likely due to the anti-angiogenic effect of these compounds. The reduction in tumor size is most likely the result of inhibition of angiogenesis mediated through the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptors located in the vascular bed of the tumor. UCLAP3 and FgM tumor cells expressed $\alpha_v\beta_5$ and therefore, in these particular tumors direct antitumor effects may contribute to tumor regression caused by inhibition of angiogenesis.

2.0 INTRODUCTION

The development of new blood vessels plays a critical role in a number of physiological and pathological events such as embryonal development, wound healing, arthritis, tumor growth and metastasis (1-4). Angiogenesis can be defined as the process by which new blood vessels form from pre-existing vessels. The process of angiogenesis consists of a cascade of interactions among microvascular endothelium, subendothelial basement membranes and perivascular stroma (5). Polypeptide growth factors released from tumor cells are believed to trigger host endothelial responses and induce angiogenesis in the progressing tumor (6,7). At least thirteen angiogenic molecules have been described (4). The role of angiogenesis in tumor progression

has been reviewed extensively (4,8). Inhibition of angiogenesis will reduce tumor perfusion, thereby cause tumor regression. Recent advances in our understanding of molecular and biochemical events that facilitate angiogenesis have provided insight into cellular invasion in general and stimulated the development of novel strategies for the treatment of diseases encompassing neovascularization (9-14).

$\alpha_v\beta_3$ integrin receptors are found on the surface of activated endothelial cells and are thought to be essential mediators of early stages of angiogenesis (15-17). Agents binding to these receptors modulate adhesion between endothelial cells and a wide variety of extracellular matrix (ECM) components. Since a few tissues, including certain tumors, express the $\alpha_v\beta_3$ receptor, cell lines used in this study were selected for their lack of $\alpha_v\beta_3$ receptor expression. This allowed the test compounds to selectively target the vascular compartment of the tumor, eliminating the potential for direct $\alpha_v\beta_3$ mediated cytotoxic effects on the tumor tissue. EMD 85189 and 121974 are $\alpha_v\beta_3$ (18,19) and $\alpha_v\beta_5$ antagonists (20,21) and were shown to inhibit the process of angiogenesis in several models. Both are cyclic peptides of the same structure, they differ in EMD 85189 being the hydrochloride of the inner salt EMD 121974 (22). Potency has been shown to be the same for both in-vitro receptor binding and cell adhesion regarding $\alpha_v\beta_3$ and $\alpha_v\beta_5$ (21,22). EMD 69601 is very similar in structure but modified so it is inactive in-vitro and therefore a suitable negative control for in-vivo experiments (20-22).

The chorioallantoic membrane of the chick embryo is composed of two separate membranes, the chorion and the allantois, that fuse early (days 4 to 5) during embryonal development. The CAM is the major respiratory structure

for the exchange of gases and nutrients during embryonal development and thus becomes highly vascularized. Studies indicate that the vascular development within the CAM begins to slow and is essentially completed during days 11 to 14 of development (23-25). The chick CAM provides a tissue composed of numerous blood vessels making it an ideal microenvironment in which to study angiogenesis.

* * * *

APPENDIX 25 — FAX SUMMARY OF PRESENTATION BY MERCK SCIENTISTS DRS. PERSCHL AND GOODMAN AT THE NATIONAL CANCER INSTITUTE RE PROPOSAL FOR CLINICAL TRIALS OF EMD-12

c/o MERCK
Merck KGaA Darmstadt Deutschland

TELEFAX

To: Dr. James M. Pluda
National Cancer Institute

Fax No.: (0 01) 3 01-4 02-04 28

Date: October 20, 1998

From: Yvonne Skaznik
Therapeutic Area Oncology

Phone No.: (++49) 6151-726492

Fax No.: (++49) 6151-726905

Total number of pages including cover sheet: 3

Dear Dr. Pluda;

Enclosed please find the summary of the Cyclopeptide presentation of Dr. Perschl and Dr. Goodman on October 26 at the NCI.

Sincerely,

Merck KGaA
s/ Skaznik
Yvonne Skaznik
Secretary Therapeutic Area Oncology

Summary

The development compound EMD 121 974 is the inner salt of a cyclized pentapeptide (c-[Arg-Gly-Asp-DPhe-(NMeVal)]. The molecular formula is $C_{27}H_{40}N_8O_7$ with a molecular weight of 588.7 g/mol.

EMD 121 974 is a potent and selective $\alpha_v\beta_3$ as well as $\alpha_v\beta_5$ vitronectin receptor antgonist. In receptor binding experiments binding experiments half maximal inhibition (IC_{50}) of $\alpha_v\beta_3$ to vitronectin was around 1 nM and around 140 nM for $\alpha_v\beta_5$. The IC_{50} of EMD 121 974 for the $\alpha_{IIb}\beta_3$ platelet receptor to fibrinogen was about three orders of magnitude higher. Inhibition of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ mediated cell adhesion with EMD 121 974 was found with low micro molar IC_{50}. In addition to inhibition of cell adhesion, migration of endothelial cells was also blocked by EMD 121 974 with low micro molar IC_{50}'s. No inhibition of platelet aggregation could be detected with a concentration tested up to 10 µM. The predecessor peptide EMD 85189, the hydrochloride salt of EMD 121 974, cross-reacted with vitronectin receptors in various species. The activity of EMD 85189 and EMD 121 974 on human cells *in vitro* was shown to be identical.

EMD 121 974 has been shown to inhibit tumor growth in various *in vivo* systems including chicken chorioallantoic membrane model (CAM), nude mice and SCID / human skin chimeric mice inoculated with human tumor cells. Cytokine induced angiogenesis in a CAM model was inhibited by EMD 121 974 in a dose dependent manner. Moreover, growth inhibition of tumors derived from human tumor cells was observed in a CAM tumor model. In nude mice inoculated

with human tumor cells EMD 121 974 inhibited tumor growth rate in a variety of different dose regimens and treatment schedules. A similar effect of EMD 121 974 was observed in SCID / human skin chimeric mice. Human neonatal foreskin transplanted on the back of these animals was inoculated with human tumor cells. It was found that EMD 85189 (hydrochloride form of EMD 121 974) inhibited tumor growth compared to control-treated animals. In some experiments, the innoculated tumor cells did not express α_v-integrin demonstrating that the effects of the inhibitors on the integrin receptors are not via the tumor cells in these experimental systems. Optimal anti-tumor anti-angiogenic activity *in vivo* was achieved with doses of 10-15 mg/kg. Together with the animal tumor models, the other experimental system suggested that EMD 121 974 inhibited angiogenesis.

Differences in plasma elimination half-lifes of EMD 121 974 among species were observed. In mice the drug was eliminated with $t_{1/2}$ of 0.3h, whereas in cynomolgus monkeys $t_{1/2}$ was 1.1h. Binding to serum proteins demonstrated that 61%, 26-42%, and 22%. of EMD 121 974 bound to plasma proteins from mouse, monkey, and man, respectively. The majority of EMD 121 974 was cleared as unchanged drug, in mice predominantly via the intestinal tract, and in monkeys to a larger extent via the renal route. The radioactive drug did not accumulate significantly in organs and tissues in mice. The highest concentrations was detected in liver followed by kidneys.

An acute toxicity study in mice with single intravenous administration of EMD 121 974 resulted in a median lethal dose (LD50) of 239 mg/kg for both sexes with deaths occurring immediately after iv injection.

EMD 121 974 was tolerated in a 7-day and a 28-day study in mice with daily iv bolus injections of doses up to 90 mg/kg body weight. The clinical and clinico-chemical alterations were slight and produced no signs of systemic toxicity. The pathological evaluations of these studies did not produce any pathomorphological evidence of local or systemic toxic effects of EMD 121 974.

Cynomolgus monkeys received daily iv injections of 10, 30 and 90 mg/kg EMD 121 974 body weight for four weeks. Animals treated with 90 mg/kg showed behavioral changes (transient hypoactivity, sluggishness, lateral/prone position) as well as moderate to marked anemia and reticulocytosis in male and especially in female animals. At 90 mg/kg pallor of the inner organs was noted in female animals, an alteration which was not associated with any histopathological finding. These treatment-related changes proved to be fully reversible at the end of the recovery period.

No signs of a mutagenic potential were found with EMD 85189 in a bacterial mutagenicity test with and without a metabolizing system and with EMD 121 974 in an in vitro gene mutation test in mouse lymphoma cells.

The following additional toxicity studies are planned:

- Repeated dose toxicity:
  - 6 months toxicity, mice, ip injection b.i.d (start: 10/98)
  - 9 months toxicity, Cynomolgus monkey, 1 hour iv infusion 3 x /week (start: 11/98)

- Reproductive toxicity (start: 01/99)
  - male and female fertility
  - embryotoxicity

- Genotoxicity (start: 11/98) .

A clinical Phase I study has started including patients with solid tumors not amenable to established forms of treatment. Patients receive a 1 hour infusion twice weekly for four consecutive weeks. The scheduling is based on preclinical results demonstrating effectivity in mice treated every other day despite a short plasma half-life. Starting dose for the first three patients was 30 mg/sqm (approximately 1/10 of the estimated MTD in mice). Pharmacologically guided dose escalation is applied to identify a safe dose range, and to date, 6 patients have been treated with EMD 121 974 without major drug related toxicities. Nausea (grade 1) has been reported in two patients, and vomiting (grade 1), headache, and diarrhea (grade 2) in one patient.

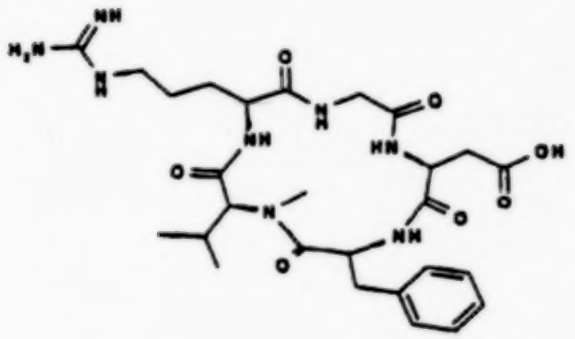
Available data from preclinical experiments indicate that the angiogenesis inhibitor EMD 121 974 could be suitable for the

treatment of solid tumors. Its use in man does not appear to be associated with an unacceptable risk.

EMD 121 974

Summary

The development compound EMD 121 974 is the inner salt of a cyclized pentapeptide (c-[Arg-Gly-Asp-DPhe-(NMeVal)] . The molecular formula is $C_{27}H_{40}N_8O_7$ with a molecular weight of 588.7 g/mol.



EMD 121 974 is a potent and selective $\alpha_v\beta_3$ as well as $\alpha_v\beta_5$ vitronectin receptor antagonist. In addition to inhibition of cell adhesion, migration of endothelial cells was also blocked by EMD 121 974. The predecessor peptide EMD 85189, the hydrochloride salt of EMD 121 974, cross-reacted with vitronectin receptors in various species. The activity of EMD 85189 and EMD 121 974 on human cells *in vitro* was shown to be identical.

EMD 121 974 has been shown to inhibit tumor growth in various *in vivo* systems including chicken chorioallantoic membrane model (CAM); nude mice and SCID / human skin chimeric mice inoculated with human tumor cells. Cytokine induced angiogenesis in a CAM model was inhibited by EMD 121 974 in a dose dependent manner. Moreover, growth inhibition of tumors derived from human tumor cells was observed in a CAM tumor model. In nude mice inoculated with human tumor cells EMD 121 974 inhibited tumor growth rate in a variety of different dose regimens and treatment schedules. A similar effect of EMD 121 974 was observed in SCID / human skin chimeric mice. Human neonatal foreskin transplanted on the back of these animals was inoculated with human tumor cells. It was found that EMD 85189 (hydrochloride form of EMD 121 974) inhibited tumor growth compared to control-treated animals. In some experiments, tumor cells which did not express αv integrin were inoculated, demonstrating that the effects of the inhibitors on the integrin receptors were not via the tumor cells in these experimental systems. Together with the animal tumor models, the other experimental systems suggested that EMD 121 974 inhibited angiogenesis.

The majority of EMD 121 974 was cleared as unchanged drug.

An acute toxicity study in mice with single intravenous administration of EMD 121 974 has been performed.

EMD 121 974 was tolerated in a 7-day and a 28-day study in

mice with daily iv bolus injections. The clinical and clinico-chemical alterations were slight and produced no signs of systemic toxicity. The pathological evaluations of these studies did not produce any pathomorphological evidence of local or systemic toxic effects of EMD 121 974.

EMD 121974

Cynomolgus monkeys received daily iv injections for four weeks.

No signs of a mutagenic potential were found with EMD 85189 in a bacterial mutagenicity test with and without a metabolizing system and with EMD 121 974 in an in vitro gene mutation test in mouse lymphoma cells.

The following additional toxicity studies are planned:

- Repeated dose toxicity:
  - 6 months toxicity, mice
  - 9 months toxicity, Cynomolgus monkey
- Reproductive toxicity
- Genotoxicity

A clinical Phase I study has started including patients with solid tumors not amenable to established forms of treatment. The scheduling is based on preclinical results demonstrating effectivity in mice treated every other day despite a short plasm half life. Pharmacologically guided dose escalation is applied to identify a safe dose range, and to date, 6 patients have been treated with EMD 121 974 without major drug related toxicities.

Available data from preclinical experiments indicate that the angiogenesis inhibitor EMD 121 974 could be suitable for the treatment of solid tumors. Its use is man does not appear to be associated with an unacceptable risk.

APPENDIX 26 — EXCERPT FROM THE IND APPLICATION FILED WITH THE FDA BY IXSYS, INC. FOR ANTIBODY "VITAXIN"

INVESTIGATORS BROCHURE

Vitaxin

(humanized LM609 monoclonal antibody)

December 30, 1996

Ixsys, Inc.
3550 Dunhill Street
San Diego, CA 92121

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6. Storage

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A. SYNOPSIS

Studies at The Scripps Research Institute have demonstrated the requirement for integrin $\alpha_v\beta_3$ in the angiogenic process (Brooks et al., Science 264: 569, 1994). These studies showed the enhanced expression of $\alpha_v\beta_3$ on newly developing blood vessels in human wound tissue with limited expression on vessels in normal tissue. Furthermore, using the chick chorioallantoic membrane (CAM) model, administration of an $\alpha_v\beta_3$ specific antibody, LM609, was shown to inhibit growth factor and tumor induced angiogenesis. The anti-angiogenic activity of LM609 was demonstrated further by Friedlander et al. (Science 270: 1500, 1995) who showed the inhibition of basic fibroblast growth factor-induced angiogenesis by LM609 in the rabbit corneal pouch model. Targeting integrin $\alpha_v\beta_3$ as a useful anti-cancer approach was suggested by the growth inhibition of $\alpha_v\beta_3$-negative tumors by LM609 in the CAM and SCID mouse/human skin models (Brooks et al., Cell 79:1157, 1994; Brooks et al., J. Clin. Invest. 96: 1995).

The Sponsor has generated a humanized version (*Vitaxin*) of LM609 whereby over 95% of the molecule is human, with an IgG_1 background. The Sponsor has performed additional preclinical models to establish its biologic activity, which are summarized in this brochure under preclinical pharmacology. Additional information on 1) chemistry and formulation, 2) preclinical toxicology and pharmacokinetics, 3) a risk benefit assessment and 4) clinical assays is also provided.

APPENDIX 27 — DEMONSTRATIVE EXHIBIT SUMMARIZING TRIAL TESTIMONY BY EXPERT WITNESS L.L. HOUSTON, REGULATORY CONSULTANT FOR IXSYS, REGARDING DATA FROM ACCUSED EXPERIMENTS "INCLUDED IN THE IXSYS IND."

Included in the IXSYS IND Submission

- data for chick CAM experiments? ☑
- data for in vitro experiments? ☑
- data for rabbit cornea experiments? ☑
- data for SCID mouse/human skin experiments? ☑
- data for non-GLP experiments? ☑

APPENDIX 28 — EXCERPTS FROM FDA'S GUIDANCE RE GLP REGULATIONS

CENTER FOR DRUG EVALUATION AND RESEARCH

GUIDANCE FOR INDUSTRY

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder//guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,
FOOD AND DRUG ADMINISTRATION

[1] GOOD LABORATORY PRACTICE REGULATIONS

QUESTIONS AND ANSWERS

Since June 20, 1979, the agency has been asked many questions on the Good Laboratory Practice regulations (GLPs, 21 CFR 58). In accord with agency procedures, responses have been prepared and copies of the associated correspondence have been filed in the Dockets Management Branch (HFA-305). The responses have also been provided to the bioresearch monitoring program managers and to the district offices in order to ensure consistency of interpretation and equity of program operation. Unfortunately, the numerous filed correspondences contain many repeat questions that are not categorized to relate to the specific GLP subpart and section. On occasion, the answers appear to be somewhat cryptic. These disadvantages serve to limit the utility of the correspondences as advisories to our headquarters and field offices.

This document, therefore, consolidates all GLP questions answered by the agency during the past 2 years, clarifies the questions and answers as needed, and relates the questions and answers to the specific pertinent provisions of the GLPs. It represents a digest of some 30 letters, 160 memoranda of telephone conversations, 34 memoranda of meetings and 30 miscellaneous correspondences that have been issued by agency personnel. The document does not duplicate questions and answers that were dealt with in the August, 1979 Post Conference Report on the Good Laboratory Practice Regulations Management Briefings.

This document should be reviewed by field investigators prior to making GLP inspections and by headquarters personnel involved in the GLP program. Questions should be directed to:

Dr. Paul D. Lepore
Bioresearch Monitoring Staff, HFC-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
301-443-2390

[2] SUBPART A

GENERAL PROVISIONS

Section 58.1 Scope.

1. Do the GLPs apply to validation trials conducted to confirm the analytical methods used to determine the concentration or test article in animal tissues and drug dosage forms?

   No.

2. Do the GLPs apply to the following studies on animal health products: overdosage studies in the target species, animal safety studies in the target species, tissue residue accumulation and depletion studies, and udder irritation studies?

   Yes.

3. Do the GLPs apply to safety studies on cosmetic products?

   No. Such studies are not carried out in support of a marketing permit. However, the GLPs represent good quality control; a goal that all testing facilities should strive to attain.

4. Do safety studies done to determine the potential drug abuse characteristics of a test article have to be done under the GLPs?

   Yes they do, but only when the studies are required to be submitted to the agency as part of an application for a research or marketing permit.

5. Do the GLPs apply to the organoleptic evaluation of processed foods?

   No.

6. Do the GLPs apply to all of the analytical support work conducted to provide supplementary data to a safety study?

   The GLPs apply to the chemical procedures used to characterize the test article, to determine the stability of the test article and its mixtures, and to determine the homogeneity and concentration of test article mixtures. Likewise, the GLPs apply to the chemical procedures used to analyze specimens (e.g. clinical chemistry, urinalysis). The GLPs do not apply to the work done to develop chemical methods of analysis or to establish the specifications of a test article.

7 Is it possible to obtain an exemption from specific provisions of the GLPs for special nonclinical laboratory studies?

* * *

[4]

4. A laboratory conducts animal studies to establish a baseline set of data for a different test species/strain. No test article is administered but the toxicology laboratory

facilities and procedures will be used and the resulting data may eventually be submitted to the agency as part of a research or marketing permit. Are the studies considered to be nonclinical laboratory studies that are covered by the GLPs?

Generally, a nonclinical laboratory study involves a test article studied under laboratory conditions for the purpose of determining its safety. The cited example does not fit the definition so it would not be covered by the GLPs. Since the data from the baseline studies may be used to interpret the results of a nonclinical laboratory study, it is recommended, but not required, that the study be conducted in accord with GLPs in order to ensure valid baseline data.

5. The definition of "nonclinical laboratory study" excludes field trials in animals. What is a field trial in animals?

   A field trial in animals is similar to a human clinical trial. It is conducted for the purpose of obtaining data on animal drug efficacy and it is excluded from coverage under the GLPs.

* * * *

APPENDIX 29 — EXCERPTS FROM OFFICIAL FDA PUBLICATION ENTITLED "GUIDANCE FOR INDUSTRY: GOOD LABORATORY PRACTICE REGULATIONS," PUBLISHED AUGUST 1979, REVISED NOVEMBER 1998

GUIDANCE FOR INDUSTRY

GOOD LABORATORY PRACTICE REGULATIONS

MANAGEMENT BRIEFINGS

POST CONFERENCE REPORT

U.S. Department of Health and Human Service

Food and Drug Administration

Office of Regulatory Affairs

August 1979

(Minor editorial and formatting changes made November 1998)

* * *

24. Does the Agency agree that the GLPs are applicable to safety studies intended for submission to the Agency in support of the approval of a regulated product and that they are not applicable to preliminary exploratory studies, screening studies, and range-finding studies whose purpose is to develop or improve the experimental design of a planned nonclinical laboratory study?

Yes.

* * *

38. Does the term "nonclinical laboratory study" include animal laboratory studies, which are designed for the explicit purpose of determining whether a test article has reasonable promise of clinical effectiveness, and in which observations bearing on clinical safety are only incidental or fragmentary, or at most, clearly secondary?

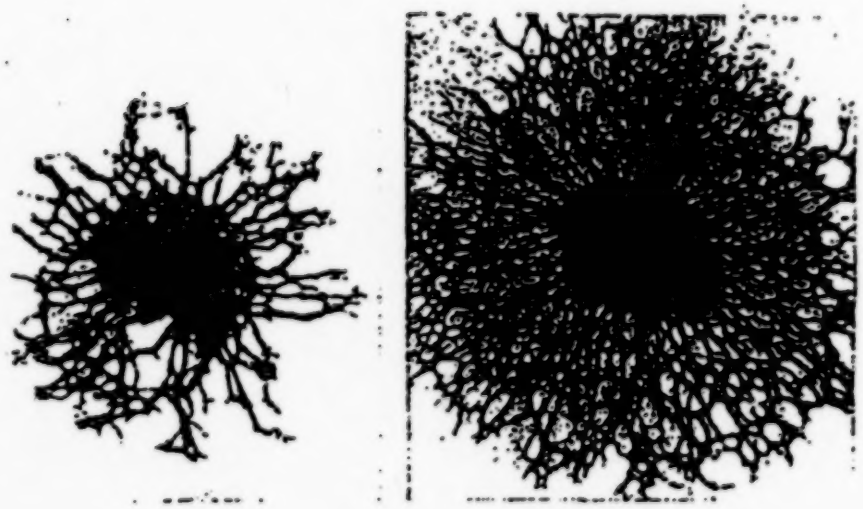
No

* * * *

APPENDIX 30 — EXCERPT FROM GRANT APPLICATION ENTITLED "ROLE OF VNR INTEGRINS IN OCULAR ANGIOGENESIS"

Merck, KGaA Sponsored Program on

Role of VNR Integrins in Ocular Angiogenesis



Friedlander Laboratory
Department of Cell Biology
The Scripps Research Institute
Pre-IND Filing Report and Summary
June 5,1997

Angiogenesis Project Personnel,
Friedlander Laboratory

Martin Friedlander, M.D., Ph.D., Principal Investigator

Edith Aguilar M.D., Post-doctoral Fellow, animal models, animal surgery; human tissue immunohistochemistry.

Miyuki Sugita, M.D., Post-doctoral Fellow, animal models, animal surgery, human tissue immunohistochemistry.

Xianjin Yi, M.D., Ph.D., Post-doctoral Fellow, animal models, animal surgery, molecular biological analysis of cell-cell interactions during retinal vasculogenesis, molecular therapeutics.

Chandra Theesfeld, B.S., principal Research Technician II, animal models, scanning laser confocal and computer assisted analyses, molecular genetics.

Christine Kincaid, B.S., Research Technician I, animal. models.

Robert Shafer, A.B., Research Technician I, animal models, computer analyses.

Jennifer Jett, Research Assistant, general laboratory assistance.

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APPENDIX 31 — EXCERPT FROM INTERROGATORY RESPONSES BY SCRIPPS AND DR. DAVID CHERESH (INTERROGATORIES PROPOUNDED BY TELIOS PHARMACEUTICALS INC.)

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

Case No. 96-CV-1307 K AJB

TELIOS PHARMACEUTICALS, INC., a Delaware corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,

Plaintiff,

V.

MERCK, KGaA, a German corporation, THE SCRIPPS RESEARCH INSTITUTE, a California nonprofit corporation, DR. DAVID A. CHERESH, a California citizen, and DOES 1-25 inclusive,

Defendants.

RESPONSE TO FIRST SET OF INTERROGATORIES TO DEFENDANTS SCRIPPS RESEARCH INSTITUTE AND DR. DAVID A. CHERESH FROM PLAINTIFF TELIOS PHARMACEUTICALS. INC.

* * *

INTERROGATORY NO. 4:

State all facts on which you base your Fourth Affirmative Defense that Defendants are not infringing the '525. Patent under 35 U.S.C. §271(e)(1).

RESPONSE TO INTERROGATORY NO. 4:

In addition to the General Objections set forth above, Defendants object to this Request on the grounds that that it is premature. This action has just recently been filed, and Defendants have had no discovery of Plaintiffs.

Subject to and without waiving the objections above, Defendants respod as follows. All of the current, ongoing research activities of Dr. Sheresh which involves cyclopeptide antagonists that block angiogenesis are reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs, *i.e.*, the Food and Drug Act. In addition,k as explained below, some or all of the composition claims (8-11) of the '525 Patent are believed to be invalid under 35 U.S.C. §§102 and 103 and thus they cannot be infringed.

* * * *

APPENDIX 32 — EXCERPT FROM AGREEMENT BETWEEN LA JOLLA CANCER RESEARCH FOUNDATION AND TELIOS PHARMACEUTICALS, INC., EFFECTIVE MAY 12, 1995

AGREEMENT BETWEEN

LA JOLLA CANCER RESEARCH FOUNDATION

AND

TELIOS PHARMACEUTICALS, INC.

This Agreement is entered into as of May 12, 1995, by and between Telios Pharmaceuticals, Inc., a Delaware corporation ("Telios") and La Jolla Cancer Research Foundation, a California nonprofit public benefit corporation (the "Foundation") (collectively hereinafter referred to as the "Parties").

WHEREAS, Integra LifeSciences Corporation ("Integra") desires to acquire Telios pursuant to a Plan of Reorganization as now proposed by Telios and filed with United States Bankruptcy Court for the Southern District of California (the "Plan"); and

WHEREAS, included among Telios' assets are certain intellectual property rights granted to Telios by the Foundation pursuant to that certain License Agreement for Adhesion Peptides Technology, dated June 24, 1987, as amended by the letter agreement dated February 5, 1992 ("License Agreement"), that certain First Refusal Agreement for Technology entered into as of June 24, 1987 ("First Refusal Agreement"), and that certain First Refusal Agreement for Technology (Amended and Restated) dated

as of October 10, 1991 ("First Refusal Agreement (Amended and Restated)") (the First Refusal Agreement and First Refusal Agreement (Amended and Restated) are sometimes collectively referred to as "First Refusal Agreements"); and

WHEREAS, the Parties hereto desire to encourage the development of technologies covered by the License Agreement ("Licensed Technology") and the First Refusal Agreements and to facilitate confirmation of the Plan by resolving between them any potential disagreements pertaining to the character and extent of rights held by Telios and flowing to Integra by virtue of the Plan;

NOW, THEREFORE, for and in consideration of the mutual and respective promises made herein, the Parties intending to be legally bound hereby, agree as follows:

1. *Assumption and Assignment of License Agreement by Telios*. On the closing date of the acquisition of Telios by Integra contemplated by the Plan ("Closing Date"), Telios shall assume the License Agreement under 11 U.S.C. §365 and may assign the License Agreement to Integra. The Foundation consents to such assumption and assignment. If an alternative procedure for transferring Telios' rights under the License Agreement to Integra is proposed by Telios, such as having the Foundation and Integra enter into a new license agreement, the Foundation shall reasonably cooperate with Telios.

APPENDIX 33 — TRIAL TESTIMONY: CROSS EXAMINATION OF MICHAEL D. PIERSCHBACHER, PH.D., SENIOR VICE-PRESIDENT OF INTEGRA CORP. AND CO-INVENTOR OF PATENTS IN SUIT, CALLED BY PLAINTIFFS ON FEBRUARY 14, 2000

[Commencing at page 487]

Q. Well, you knew that you had never given Dr. Cheresh a license under any of your patents, right?

A. That's correct.

Q. You knew after 1988 you hadn't authorized him to use any of your patented technology, right?

A. I'm not sure exactly what you mean by "authorized." We had no written agreement between Dr. Cheresh and Telios, no.

Q. You hadn't given him approval to do what he was doing in his laboratory.

A. Our agreement with Burnham expressly required that we — that Telios — allow basic research with the technology to go forward.

Q. You didn't ever discuss that agreement with Dr. Cheresh, did you?

A. Not to my recollection, no.

Q. All right. And after December of 1994, you knew that Dr. Cheresh was using cyclic peptides to inhibit angiogenesis, correct?

A. After what time frame?

Q. December of 1994.

A. Yes.

Q. And you knew that because you read his Cell paper that was published in December 1994.

A. That's correct.

* * * *

APPENDIX 34 — TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS SHOUKAT DEDHAR, PH.D., SCIENTIST, CALLED BY PLAINTIFFS ON FEBRUARY 16, 2000

[Commencing at page 846]

* * *

Q. Does that claim cover peptides that have amino acids in both the L- and the D-form?

A. Yes.

Q. Now, I'd like to turn your attention to certain peptides that were contained in experiments, that were used in experiments, by Scripps. You have had the opportunity to review laboratory notebooks from scientists at the Scripps Institute, have you not, sir?

A. Yes.

Q. And you have seen there that these experiments, many of these experiments, use certain peptides?

A. That's correct.

Q. And they are what we have talked about in the past as the Merck peptides?

A. Yes.

Q. Could you identify those peptides?

A. Yes. There are, by and large, three peptides involved in [847] most of the experiments. They all contain the sequence arginine-glycine-aspartic acid.

Q. That's RGD?

A. That's RGD. The names of the peptides are 66203, which has the sequence. It's a cyclic peptide with the sequence RGD D-form of phenylalanine followed by valine, and it's an acid form. The other peptide, the next peptide is 85189, which has the same sequence. It is a cyclic peptide containing RGD D-form of phenylalanine, and in this case N-methyl valine. So the valine is modified. And, again, it is a hydrochloric acid form. And then 121974 is similar to the 85189 except that this is an inner salt. It is a salt form. These were the three peptides that were used in most of the experiments. I also came across two other peptides — 62184, which is a trifluoracetate salt form, and 80838, which was modified with a fluorescein tag for certain experiments.

Q. Now, you characterize these peptides as cyclic peptides?

A. Yes.

Q. Could you explain to the jury what that means?

A. Well, the peptide is synthesized in such a way that it would form a head-to-tail bond and form — become cyclic. I'm not a peptide chemist and I couldn't tell you exactly how it is synthesized. But these peptides are not linear like the other RGD peptides, but they are cyclic in nature, so that — they have a different structure.

[848] Q. And all three of these Merck peptides you described were cyclic?

A. Yes.

Q. And all three of them have the sequence RGD?

A. That's correct.

Q. Followed by, what's the other amino acid?

A. It's the D-form of phenylalanine.

Q. Now, does Claim 8, as you understand it, Dr. Dedhar, cover cyclic peptides?

A. Yes.

Q. As well as linear?

A. Yes.

Q. Now, let's go back to — what was the slide number that depicted cell attachment-promoting activity?

A. Number 14.

Q. Actually, before we do that, Dr. Dedhar, have you in the literature seen publications that describe cyclic peptides that have the same sequence as the Merck peptides — RGD followed by phenylalanine in the D-form?

A. Yes, I have.

Q. And do you have that publication in front of you?

A. Yes.

Q. And that is trial exhibit number —

A. Well, there are — sorry. I have to find the paper.

Q. Would you look at trial exhibit No. 15?

[849] A. Yes, that's the paper I had in mind.

Q. Now, does this peptide — does this paper describe a peptide that is the same as any of those Merck peptides you've been talking about?

MS. THAYER: Pardon me. Your Honor, I think this exhibit may have been misdescribed for the record. Our indication is that there isn't an Exhibit 15. Could we just clear that up quickly?

MR. FLORES: Your Honor, I've been informed that the numbering has been changed on this. It is actually Exhibit AAY. We changed that number.

Q. BY MR. FLORES: So, Dr. Dedhar, so we don't get confused, take yours and change that 15 to AAY.

Do you have the question in mind?

A. No. Could you please repeat it?

Q. Does this paper, Exhibit AAY, describe a peptide that is similar to any of the Merck peptides?

A. Yes, it does.

Q. Which one?

A. It describes a peptide identical to 66203, which is a cyclic peptide with the sequence RGD followed by phenylalanine in the D-form valine.

Q. Is it the same in all other respects?

A. Yes.

Q. It's identical?

[850] A. Yes.

Q. Now, did you read the name of this paper to the jury?

A. Yes. The paper is entitled, "Arginine-Glycine-Aspartic Acid Constrained Within Cyclic Pentapeptides: Strong and Selective Inhibitors of Cell Adhesion to Vitronectin and Laminin Fragment P1."

Q. When was this paper published?

A. This paper was published in October of 1991.

Q. And who are the authors here?

A. The authors names are Monique Aumailley, Marian Gurrath, Gerhardt Muller, Johann Calvete, Rupert Timpl, and Horace Kessler.

Q. Now, does this paper describe any of the biological activity of the compound that's identical to 66 — what's that number?

A. 66203, yes.

Q. 66203?

A. Yes, it does.

Q. What does it describe about the biological activity of that compound?

A. The biological activity that was looked at in this paper was the inhibition of cell attachment to primarily vitronectin and laminin P1, both of which do contain RGD sequences.

Q. And does this paper show anything about the binding of this peptide, which I'll call 66203, since it's identical in [851] structure? Does it show anything about the binding of that peptide to an integrin receptor?

A. It doesn't show direct binding to the integrin receptor, but they carried out the inhibition of cell attachment assays. In order to inhibit cell attachment, the RGD peptide would have to bind to the receptor on the surface of the cells in order to carry out this inhibition.

Q. Does it identify which receptor it binds to on the surface of cells?

A. Yes. Alpha-v-beta-3 is certainly one receptor that has been identified, which is a receptor for vitronectin. The receptor that is involved for laminin is unknown in this case.

Q. Now, what does this paper say about the extent to which this 66203 compound will bind to alpha-v-beta-3?

A. Well, basically what this paper shows is that, by making this cyclic peptide with the sequence RGD D-phenylalanine valine, that this peptide has about 20 to a hundred fold better affinity for the receptor for vitronectin compared to the linear peptide RGD. So it shows that this is

a very potent way of — that this peptide, by making the cyclic peptide with the sequence, that the peptide acquires a much higher affinity for the receptor.

Q. Now, is this the peptide — are you familiar with the paper that Dr. Cheresh published in the journal Cell in 1994, I believe, December?

[0852] A. Yes, I am.

Q. Do you have that in front of you? I believe it's Exhibit No. 24.

A. Yes, I have the paper. Yes.

Q. Now, does this paper by Dr. Cheresh use the same peptide that was discussed in the paper published back in 1991 that's Exhibit AAY?

A. Yes, it does.

Q. And what does Dr. Cheresh use it for as described in his 1994 Cell paper?

A. In the 1994 Cell paper, this peptide, which is actually called 66203, cyclic RGD D-phenylalanine valine, the peptide in this case is used for the inhibition of angiogenesis using an assay, which is called the CAM assay, which we'll go into detail later perhaps.

Q. Does Dr. Cheresh's Cell paper, does the work described there use the peptide published back in 1991, 66203, to bind to alpha-v-beta-3?

A. Yes.

Q. And does Dr. Cheresh's paper refer back to this 1991 publication by Monique Aumailley, et al.?

A. Yes, it does. On the —

Q. Where does it do that?

A. On the first page of the paper, in the Results section. Should I read the sentence?

[853] Q. Why don't you read that, the sentence that refers back to the 1991 Aumailley paper.

A. It states that the RGD D-phenylalanine valine peptide has been previously shown to preferentially inhibit ligand binding or cell adhesion events mediated by alpha-v-beta-3, in brackets, Aumailley, et al., 1991. And in the back this paper is referenced as the one that we spoke about earlier, the Exhibit AAY.

Q. Now, Dr. Cheresh wrote here that this peptide, 66203, had been previously shown to preferentially inhibit ligand binding or cell adhesion events mediated by alpha-v-beta-3.

A. That's correct.

Q. Would you explain what that means?

A. Well, it means that this peptide blocks or binds to the receptor alpha-v-beta-3 that is found on the surface of a variety of cell types. And by binding to that receptor, it prevents the cells from binding to vitronectin in this case. So you have ligand binding — ligand in this case is vitronectin — so the peptide prevents the cell or the receptor from binding to the ligand, vitronectin, and, by so doing, inhibits cell attachment.

* * * *

APPENDIX 35 —TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS SHOUKAT DEDHAR, PH.D., SCIENTIST, CALLED BY PLAINTIFFS ON FEBRUARY 17, 2000

[Commencing at page 940]

* * *

Q. Was that understood back in 1983?

A. Yes, it was.

Q. Now, on another subject, Dr. Dedhar, were there experiments that you saw in those Scripps notebooks that involved the testing of organic molecules that do not have the RGD sequence in them?

A. Yes, I did.

Q. And what kind of — what types of tests were applied to those kinds of substances?

A. The organic molecules that were used in three types of experiments, the chick CAM assay, which I demonstrated earlier, the angiogenesis chick CAM assay, the cell adhesion assay, where the cells are allowed to attach to an extracellular matrix protein and molecules are added to see if they will inhibit that attachment, and also in the chick CAM tumor assay, [941] where the tumor cells are applied to the CAM and then compounds are added. Those were the three categories of experiments where those organic compounds were used.

Q. And those organic compounds did not have an RGD sequence?

A. No. They are organic molecules, yes.

Q Could you maybe explain the term "organic molecule"?

A. Well —

Q. In —

A. They are completely different from — they don't necessarily have the — they don't have the atoms of carbon, hydrogen, nitrogen that amino acids do. They can have very different types of atoms.

Q. Now, in these experiments, you've been describing where the non-RGD organic molecules were tested. Were RGD peptides, the three Merck peptides that we've been talking about, were they used in those experiments?

A. Yes, they were. In every case the — where these organic molecules were tested in these types of experiments, the RGD peptides, the three Merck peptides, were used as positive controls. So we talked about positive control this morning, and because it was known how these RGD peptides work, and they did work, so in the CAM assay it was known that the RGD peptides would inhibit angiogenesis. So they were used as a positive control to determine whether these organic compounds had the same effect or worked or not. Because if they didn't [942] use those positive controls, then they would never know whether the test compounds, the organic compounds, worked or not. So they used those as positive controls in each of those assays.

Q. Were the organic — the non-RGD organic molecules that were tested, the unknown or the known substances in those experiments?

* * * *

APPENDIX 36 — TRIAL TESTIMONY: DIRECT EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY PLAINTIFFS ON FEBRUARY 22, 2000

[Commencing at page 1085]

* * *

Q. The discovery that RGD compounds are useful as antagonists to alpha-v-beta-3 in your mind had nothing to do with your [1086] method?

A. Well, that's correct, because we actually made our original discovery and published that in Science in April of '94 without using any RGD peptides at all. In fact, there wasn't an RGD peptide used in that Science paper. Rather, we used an antibody that was an antagonist of alpha-v-beta-3. And with no RGD peptide there in that study showed very definitively that alpha-v-beta-3 antagonism or the inhibition, in this case with an antibody, could block angiogenesis.

Q. Well, it was your discovery, sir, correct, that if you inhibit alpha-v-beta-3, you can inhibit angiogenesis.

A. That's correct. We did that with an antibody. So that was really our major discovery. That was when we knew what we had.

Q. But as the invention, claimed in this patent, requires the use of an RGD peptide to accomplish the inhibition of alpha-v-beta-3, correct?

A. Well, there were two patents written, as I recall, and one of them — one of them, which was the second one, gave

examples of peptides that contained the RGD peptide or RGD sequence that could be used as an antagonist, like LM609 could be used to block angiogenesis.

Q. And that's this patent right here, isn't it, the '591?

A. Where are you referring to? I'm not sure the number of the patents actually.

[1087] Q. No, I'm talking about the number of the patent itself, Exhibit 77, the '591 Patent.

A. Yes, that's correct.

Q. And in this '591 Patent, you show how RGD peptides can be used to inhibit angiogenesis.

A. Well, once again, we show a very select, specific example of an RGD peptide.

Q. Right. And that example was the 66203.

A. I believe so.

Q. That was the one that was shown in the Aumailley paper.

A. That's correct.

Q. And I understand and appreciate your pointing out that there is an antibody patent, but with respect to this, the invention claimed in this particular patent as described, the use of RGD peptides is central to the method, isn't it.

A. Well, I was really referring back to your original

question, which had to do with whether or not RGD peptides were an essential part of my discovery. And I was simply answering the fact that, no, they weren't any part of the discovery, because the discovery was made with an antibody that has no RGD sequence within it. We later used — went back to the literature and realized that there were peptides out there that we could employ and to prove our point. Quite often, as scientists, we like to see more than one example of an observation.

[1088] So, for example, if we have an antibody that can do the job, we'd like to see that other classes of molecules have the same function. This supports our contention that it is, in fact, alpha-v-beta-3 that is directly contributing to angiogenesis. So we had the example of antibody. We developed the examples here with the cyclic peptides. And then ultimately went on to show that even organic molecules that had alpha-v-beta-3 inhibitory activity could do the same thing. The three of those things together make a very strong scientific case that, indeed, alpha-v-beta-3 is essential for angiogenesis.

* * *

[1116] * * *

Q. Now, wasn't there a specific provision in the 1995 agreement between Scripps and Merck where Scripps agreed to screen a specific number of compounds a year that were provided by Merck? I think it was a hundred compounds.

[1117] A. I think we had a certain limitation on the number of compounds that we could — that we would screen.

The goal, from our point of view — the answer is yes. The goal, from our point of view, was to limit this so that we weren't a screening facility, but rather a research facility that, in some cases, have to screen through some compounds to get to some answers of questions.

Q. But Merck did want to use Scripps in part as a screening facility. They wanted that service from Scripps, didn't they?

A. We, they wanted — no, I think they wanted us to be able to use our expertise with a limited number of compounds. When one really does screening, you're talking of hundreds and hundreds, if not thousands — if not millions of compounds. That's what screening is all about. In fact, I believe Merck does screening of hundreds of thousands of compounds, if not millions of compounds. I've seen their facilities. So we would not be doing what one would generally think of as screening drug candidates. That was not our goal.

Q. Well, would you take a look at a page 01037 in the 1995 agreement. Now that talks about a provision of in vitro and in vivo testing capacity for more than 100 compounds per year selected by Merck.

A. Yeah, but, once again, a hundred compounds or two hundred compounds per year are not on the scale that we think of as screening. So the goal here was to be able to put in place [1118] reagents and appropriate drug candidates to take further. And so we had a panel to refine. We didn't have the final choice. And one of the goals was to have a limited screen to examine that.

* * *

APPENDIX 37 — TRIAL TESTIMONY: CROSS EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY PLAINTIFFS ON FEBRUARY 17, 2000

[Commencing at page 1181]

* * *

CROSS-EXAMINATION

Q. BY MS. THAYER: Dr. Cheresh, do you have Exhibit 77 up in front of you?

A. Yes, I do.

Q. It's the '591 Patent.

A. Yes, I do.

Q. Do you recall you were asked the question about the Background section of that patent?

A. I recall I was asked a question about the Background, yes.

Q. Dr. Cheresh, can you turn to that Column 1?

A. Yes. I'm there now.

Q. All right. Did you actually write the Background section [1182] of this patent?

A. No, I did not.

Q. Who did?

A. The lawyers at Scripps.

Q. All right. I'd like you to focus your attention on this last paragraph here that starts "for discussions." It's Column 1.

A. Yes.

Q. Line 57.

A. Yes.

Q. Did you provide the patent attorneys with any information concerning that paragraph?

A. No, I did not.

Q. As of the filing of this patent application, had you read any of the patents that are listed down here in Column 1?

A. No, I did not.

Q. As of the time of the filing of this application, did you know who owned any of those patents?

A. No, I did not.

Q. Had you analyzed any of those patents?

A. Absolutely not.

Q. Had you discussed any of those patents with Merck?

A. No, I did not.

Q. You were asked whether or not you had ever published any of the results of research concerning non-peptide inhibitors of [1183] alpha-v-beta-3. Do you recall that?

A. Yes, I do.

Q. Have you published any in that research?

A. Yes. There was actually a paper published in, I believe it was 1998, in collaboration with Dr. Nicolaou, and this is pertaining — and also in collaboration with some of the Merck scientists. And this is involving our identification of some novel organic structures that could block alpha-v-beta-3 function.

Q. All right. Could you turn, then, to, I believe it's Exhibit 46, that is the research and — Research Funding and Option Agreement from 1995.

A. I have it here.

Q. Would you turn to the page that has the numbers MO 1039?

A. Yes.

Q. Remember you were asked some questions about these numbers?

A. Yes, I do.

Q. And you were asked some questions about screening of compounds. Do you recall that?

A. Yes, I do.

Q. Do you know whether or not the number that's there under Dr. Nicolaou's column has anything to do with screening of compounds?

A. In fact, it doesn't. It's essentially most, if not all, [1184] used for the synthesis of compounds. And I believe he developed a total of four to five compounds during that time.

Q. Now, in fact, during the course of the 1995 Research and Funding Agreement — by the way, how long did that agreement last?

A. The '95 agreement?

Q. Yes.

A. Three years.

Q. All right. During the course of that time, how many total compounds, organic compounds, developed either by Merck or by Dr. Nicolaou, did you test in your laboratory either in vitro or in vivo?

A. I think it was a total of no more than 15 to 20.

Q. And, of those, about how many were tested in the chick CAM experiments?

A. I would say roughly half, maybe eight to 12 at the most.

* * *

[1187] * * *

Q. Now, prior to this letter, prior to July 1994, had you communicated to Merck any of the results of your experiments with the chick CAM and LM609 showing that you could inhibit angiogenesis?

A. Yes. We had made them aware during the course of our experiments, as we had in the past, that inhibitors of alpha-v-beta-3, either antibodies or peptide inhibitors, had very significant effects on angiogenesis and impacted actual tumor growth. And, as I recall, they were very excited about that, that observation, and that which, of course, served as the basis for changing the direction of the future funding.

Q. Prior to this paper in July of 1994, had you communicated to Merck the data showing that EMD 66203 could cause tumor [1188] regression?

A. Yes. We had made the observation that, when 66203 was systemically injected into the bloodstream of the chick embryo, that it blocked the blood supply, but also the tumor shrank.

We communicated that to the Merck people, and they, of course, were very excited. And this served as the basis for our publication in Cell of that year.

Q. Now, throughout the summer of 1994, did anyone from Merck indicate to you that Merck had lost interest in funding your research?

A. Absolutely not. In fact, it was clear to me that they had an intense interest. It was just the direction had to be re-evaluated and the movement was clearly in the right direction, as far as we were concerned.

Q. All right. You were also shown an exhibit of December 1994, do you recall that, Dr. Jonczyk's letter to you?

A. Which one is it?

Q. I'm sorry. I don't have the exhibit number.

A. I think I see it here. Is it number 31, I believe it is?

Yes.

Q. 31? It's a letter dated December 20, 1994 to you from Dr. Jonczyk?

A. Oh yes. I see that here.

Q. Now, was this December letter a response to your July 1994 letter that was previously marked Exhibit 376?

[1189] A. No, it wasn't. No, it wasn't. This was a letter that resulted — it came after many, many discussions. It also included a trip to Germany where we discussed the new proposal for research to be funded. And this was then a letter summarizing some of the many discussions we had over that period of time. I think there was about six months of discussion.

Q. All right. Now, after this December 1994 time frame, did you make a proposal to Merck with respect to a program to conduct preclinical experiments at Scripps?

A. Yes, I did. I believe it was in February of '95, three months or so after this letter, because at that point I had a pretty good understanding of what it was we wanted to accomplish and what we were in position to accomplish. And so I made a proposal to them in February of that next year, of 1995.

Q. Can you take a look at Exhibit TD and tell me whether or not that is the proposal that you made in February of 1995?

A. That is the proposal, that's correct.

MS. THAYER: Your Honor, we would move Exhibit TD into evidence.

MR. FLORES: No objection.

THE COURT: Mark it in.

Q. BY MS. THAYER: And did Merck respond to this proposal?

A. Yes, they did. I think shortly thereafter they responded [1190] in a very favorable way and essentially supported essentially everything we had proposed to do at that point.

Q. I'm going to hand you what's been marked as Exhibit TI. Can you identify for the record what that is?

A. That's a letter from Dr. Sombroek to myself, and it was dated February 20th, 1995, where he has — he is saying to me that it is a pleasure for me to inform you that, within the pharmaceutical division of E. Merck, we have come to an agreement to sponsor the program on angiogenesis as described in your proposal, Scripps/E. Merck program, on angiogenesis. So the proposal that I had submitted to them on February 1st of 1995 was accepted on February 20th of 1995.

* * * *

APPENDIX 38 — TRIAL TESTIMONY: DIRECT EXAMINATION OF SIMON L. GOODMAN, PH.D., DIRECTOR OF LABORATORY OF CELL ADHESION IN PRECLINICAL ONCOLOGY AT THE MERCK FACILITY IN DARMSTADT, CALLED BY DEFENDANTS ON FEBRUARY 25, 2000

[Commencing at page 1516]

* * *

Q. Now at the same time or about the time you got this role as liaison with Dr. Cheresh, did you also get a new position with respect to a drug development project then going on at Merck?

A. Yes, I did.

Q. What was that position?

A. I was brought in as a representative of the preclinical biology in the EPG or the Development Project Group.

Q. EPG is the German abbreviation —

A. ENTVICKLUNGS PROJEKT GRUPPE. That's the German for Development Project Group.

Q. Actually, Dr. Goodman, I'm going to have to ask you to wait to finish my question, because I wasn't going to elicit that German spelling and put it on the record.

A. Excuse me.

Q. I just wanted to ask you if EPG is the acronym in German for Development Products Group.

A. Yes, it is. I beg your pardon.

Q. So if it were in English it would be DPG?

A. Yes.

Q. Okay. What exactly was the EPG?

A. The EPG was and is a committee of various representatives [1517] from different departments in Merck whose role is to take a drug candidate through to the clinic and the market.

Q. And this particular EPG, what drug candidate was it set up to administer?

A. We were developing a cyclic peptide compound coded EMD 121974.

Q. Now, I think the jury has heard quite a bit about EMD 121974. The EMD, what does that stand for?

A. E. Merck Darmstadt.

Q. Was this the same EPG that was originally set up to develop EMD 85189?

A. The same people were involved, yes. It was a continuation.

Q. So a continuation, when Merck moved from developing 85189 to developing 121974, it was a continuation of that EPG.

A. That's correct.

Q. Now, institutionally, does the establishment at Merck of an EPG mark some sort of transition in the way the drug — a potential drug candidate — is referred to?

A. Yes, it does.

Q. What is the distinction? What is the program called before the EPG?

A. Before the EPG, we're talking about basic biological research, and, after the EPG, we're in transition and applied research.

[1518] Q. Is some of the work done in the development phase referred to as preclinical development?

A. Yes, it is.

Q. Or preclinical research?

A. Yes.

Q. And is some of the work done in the research phase also referred to as preclinical development or preclinical research?

A. Some is, yes.

Q. So those terms are sometimes used interchangeably; is that correct?

MR. BECKWITH: Leading. Objection, Your Honor, leading.

THE COURT: Is there an objection?

MR. BECKWITH: Leading.

MR. WEIL: Let me rephrase the question, Your Honor.

Q. BY MR. WEIL: Is the phrase, then, preclinical research sometimes used to characterize work done before the EPG is established and sometimes to characterize work done after the EPG is established?

A. Yes.

Q. What sorts of — what sorts of people at Merck participate on the EPG?

A. There are representatives from all levels, from the basic biology and chemistry, which comes under the heading of [1519] Preclinic, so I'm in the Preclinic basic biology, to the market. So we have clinical representatives, marketing people, we have regulatory affairs people, we have the people in production, we have the people in toxicity, the people who are dealing with pharmacokinetics, the whole apparatus or the representatives of the apparatus needed to get something from basic research into somebody's arm.

Q. And, again, you represented what part of the interdisciplinary group that you've just described?

A. I represented the Biological Preclinical Research.

Q. When the EPG was formed for 85189 in 1986 — excuse me — 1996, had some of the preclinical biological research already been done on that substance?

A. Yes.

Q. Let me ask you to take a look at one of the documents there. I think it should be the second or perhaps the first in the stack — second in the stack. It's been labeled Exhibit VV.

A. I have that document.

Q. Let me ask you to take a look, then, at the middle portion of the first page of VV. And there is a heading there, except I think I've just turned off our overhead projector — there is a heading there that says "preclinical." Do you see that, sir?

A. Yes, I do.

[1520] Q. We'll have that blown up in just a minute. Scanning down the list of activities there that are characterized in this document as preclinical, is it your testimony that some of the work to establish the data needed for preclinical had already been conducted?

A. Yes, that's correct.

Q. And who had conducted that work, sir?

A. It was conducted by The Scripps Institute and by ourselves.

Q. The top of this document refers to the BAT ONC.

A. Uh-huh.

Q. What is BAT ONC?

A. That's another abbreviation for Business Area Team Oncology.

Q. So BAT stands for Business Area Team?

A. That's correct.

Q. And oncology is what, sir?

A. Study of cancer.

Q. Could you turn to the last page of this document? I'm not going to ask you details about the items laid out here, but — could you tell me, in general terms, what sort of document are we looking at here, page 3 of Exhibit VV?

A. In general terms, this is a project planning document, which describes what activities in the development of the cyclic peptide are going to take place over this time scale of [1521] two years, which is shown on this document.

Q. Are many of these activities here — I'm going to try to blow it up a little bit — are many of these activities here in the left-hand column, are these, in your experience, are these activities you would call preclinical sorts of activities?

A. Yes, they are all preclinical activities.

Q. And then looking at the timeline here, I notice that all of those start or are slated to start in the beginning of 1997, first quarter 1997. Do you see that, sir?

A. Yes, I do. I would also like to correct my last — correct my last answer, because I see — I've noticed down at the bottom we have Phase I Core and Start Phase 1, which is planned start of a clinical phase, I believe.

Q. So there are items on here that go beyond the preclinical stage?

A. That's correct.

Q. Focusing, though, on the preclinical items, do you see here that the timeline doesn't show any of them starting until 1997; is that right?

A. Yes, that's right.

Q. It's right in the sense that that's what the timeline shows?

A. It's right in the sense that it's what the timeline shows, yes.

Q. Is it right in the sense of what actually took place at [1522] Merck?

A. No, it's not. It's a computer program problem.

Q. What were your personal responsibilities as a member of the EPG starting in 1998?

A. I was responsible for taking documentation from preclinical experiments and submitting that or making sure that that was put in the correct format into a computer system called MEDIS. I was responsible for telling the EPG the results of pre — relevant preclinical experiments. I was

responsible for transferring information that had come from the EPG requests that were directed to the preclinical department back to the preclinic. If those requests were experimental requests, I was responsible for attempting to make sure that the experiment was done rapidly and correctly. And I was also responsible for transmitting knowledge that the preclinic had gained from the preclinical side which might affect the development of the drug to the general, other departments, in the company via the EPG.

Q. I want to talk about a couple of those. I think I counted five separate tasks. I want to talk about a couple of those in a little more detail. You mentioned data. You mentioned the MEDIS system. What is the MEDIS system?

A. It's a computer system.

Q. And what role does it perform at Merck?

[1523] A. Stands for Medical Document Station Information System, and it's a system which is designed for compiling the massive data that you need for a submission for a drug, drug approval, to regulatory affairs.

Q. So what is the purpose of putting data or putting a document into the MEDIS system?

A. Its possible preparation for submission to — drug submission to the regulatory affairs authorities for drug development.

Q. Now, you're not an expert, are you, sir, on the specific requirements of regulators either in Europe or the United States for drug approval? Are you?

A. No, I'm not.

Q. So how did you make the decision about which documents were to be put into MEDIS and which were not?

A. This was part of the role of the EPG. I was advised by the regulatory affairs experts, the clinical experts, and the project manager to — that certain documents were relevant from the point of view of regulatory affairs for drug submission and these documents should be entered into the system.

Q. And did you follow the instructions that you received about entering those documents into the system?

A. To the best of my ability, yes.

Q. Let me ask you to take a look at a set of documents that I've put in front of you. A couple down in the pile, Exhibits [1524] Nos. 64, 65, 67 and 68.

A. I have those documents.

Q. Do you have those documents, sir?

A. I do.

Q. What are these four documents?

A. These four documents are Theradex reports. These are reports prepared by a contract research organization called Theradex, and they describe preclinical experimental activities which were taking place in Scripps Institute in the laboratory of David Cheresh.

Q. Okay. So I've got Exhibit 64 up here on the screen.

Up in the upper left-hand corner, what does that say, sir, just under Merck?

A. Are you referring to the EMD?

Q. Yes. Can you read that for the jury, please?

A. EMD 69601,85189.

Q. And those are experimental compounds; is that right?

A. Those are experimental compounds.

Q. And on Exhibits 65 and 67 there is an additional compound listed there. Can you read that third compound for us?

A. On Exhibit 65 —

Q. Can you see it on the screen?

A. Yes. I'm sorry. On Exhibits 65 and 67 I see EMD 121974 is also included on that one on the left.

Q. So are these reports related in part to the experiments [1525] we've been talking about? I'm sorry, to the compounds that we've been talking about.

A. They refer to the compounds which are, yes, part of the development program.

Q. Very good. And each of the reports has a number on it. Do you see that? Why were these reports numbered, sir?

A. Are you referring to report 1, 2, 3, 4?

Q. Yes. Thank you. For example, Exhibit 64 here, I'm indicating it says "Report 4." Why were the reports numbered, do you know?

A. Because there were four of them emitting from Theradex.

Q. Did you refer to them in Merck from time to time as Report 1, Report 2, and so forth?

A. Yes, we did.

Q. And here under "author," is there a distinction between who did the work and who prepared the report?

A. Yes, there is.

Q. Could you explain that distinction, please, sir?

A. Yes. The "authors" of the report, who have done the scientific work which is reported, and the "report prepared by" is the contract research organization representative who has actually physically put the reports into this format that we see here.

Q. And for each of the four exhibits you have in front of you right now, Reports 1, 2, 3 and 4, is Dr. Cheresh named as at [1526] least one of the authors on each?

A. Yes, he is.

Q. Were these reports that you were responsible for getting into the MEDIS system?

A. That's correct.

Q. Do you know how many Theradex reports there were in total?

A. I'm aware of six reports which were prepared by Theradex.

Q. How would you characterize the quality of those reports, sir?

A. I would characterize them — the preparation was not very good.

Q. Did Dr. Cheresh — did you have to do something about the fact that the quality was not very good?

A. We did, yes.

Q. What did you have to do?

A. Dr. Cheresh was forced to rewrite the body of the, the scientific body of the reports and the experimental descriptions, and I was forced to make major changes in the formatting of the report, so that it may have — met our documentation format requirements.

Q. Why did you and Dr. Cheresh have to go to these efforts?

A. Because the requirements for the regulatory affairs submission are set in a very, very fixed pattern, and we had to follow that pattern when we were submitting to this MEDIS [1527] documentation system that I referred to.

Q. Now, is the information in the reports that you reviewed and caused to be put into the MEDIS system, does that information contain data from non-GLP experiments?

A. Yes, it does.

Q. Does it contain information from in vitro assays?

A. No, it doesn't.

Q. Did other information that you caused to be put into the MEDIS system, data from Dr. Cheresh's labs, include in vitro data?

A. Not from Dr. Cheresh's laboratories, no.

Q. From Scripps generally, though?

A. To my recollection, there was no in vitro data from Dr. Cheresh's laboratory directly.

Q. We'll return to that question a little later. Some of the — were some of the experiments reported in the Theradex Reports the very same experiments that are now accused of infringement in this lawsuit?

A. As far as I can tell, yes.

Q. Now, at some point did you personally take steps on behalf of Merck to arrange for clinical trials of the accused compounds in the United States?

A. No.

Q. Were you involved in any way in the process of arranging for — taking steps to see that clinical trials could take [1528] place here in the United States?

A. Yes.

Q. What did you personally do in that regard?

A. I attended a meeting or I was invited to a meeting of the investigational new drugs group at the National Cancer Institute, Jim Pluda's group, sometime in, I believe it was October of 1998, together with my colleague, Dr. Astrid Perschl.

Q. Let me stop you there for just a moment. You mentioned two names. Dr., I think, Pluda?

A. Jim Pluda.

Q. Is that P L U D A?

A. That is correct.

Q. Could you also spell Dr. Perschl's name for us?

A. Yes. It's P E R S C H L.

Q. And who is Dr. Pluda?

A. Dr. Pluda is the head of the Investigational New Drugs Division or a leading character in the Investigational New Drugs Division in the National Cancer Institute.

Q. Does Dr. Pluda work for Merck?

A. No.

Q. Dr. Perschl, who is that?

A. Dr. Perschl is a person at approximately my level in the clinical department, clinical research department, in Merck.

Q. And what was it, you said you attended a meeting with Dr. [1529] Perschl and Dr. Pluda?

A. Yes. Dr. Perschl and I were invited to the NCI to give a presentation to the NCI committee and to the Investigational New Drugs Group concerning the characteristics of the compound EMD 121974.

Q. Could you take a look, sir, at the document in front of you marked Exhibit ZP.

A. I have that document.

Q. What is Exhibit ZP, can you tell me?

A. This is a fax from Dr. — to Dr. James Pluda from Yvonne Skaznik, who is a part of — who is a member of Merck. And it shows a summary of the data that we intended to present later the same week — it is dated October 20, 1998 — at the NCI, later on, a couple days from the —

THE REPORTER: I'm sorry. I didn't catch that, sir.

THE WITNESS: It is a hard copy of data that we were going to present as a seminar presentation at that meeting.

Q. BY MR. WEIL: This doesn't appear to be just charts and graphs. When you say data, what is it you mean generally when you say "data" with respect to this document?

A. It's a description of the preclinical characteristics of EMD 121974, so it describes — on the back there is a summary of the biology — some of the chemistry and some of the, a brief report of the toxicology and the activity of the substance in these integrin assays, which I described, and in [1530] CAM assays and in tumor assays. So it is a little summary of the biological activity that we had found that we thought was relevant for the submission to the nomination of the EMD 121974 as a drug for use by the NCI.

Q. And what is it that you hoped the NCI would agree to do as a result of this meeting?

A. We hoped that the NCI would give their approval and support because they are one of the world's leading cancer therapeutic organizations, and Pluda's group see nearly all interesting new cancer drugs, and we were hoping that we would get their support for taking this drug through studies in America.

Q. Were you also seeking their active involvement in that process?

A. Yes, we were.

Q. You mentioned in summarizing some of the contents of this data CAM tests, mice tests, and so forth. Did this document in summarizing impart data provided to you from Scripps researchers?

A. That's correct.

Q. Including Dr. Cheresh.

A. That is correct.

Q. You were at this meeting; is that right?

A. Yes, I was.

Q. Did you actually present the data that's summarized here [1531] in about four pages of this memo to Dr. Pluda, this fax to Dr. Pluda?

A. Yes, we presented this data to the NCI.

Q. And you talked about those experiments?

A. In detail, yes.

Q. Did you tell them where the data came from?

A. I believe I cited Dr. Cheresh as a scientific colleague, that the information came from his laboratory, yes.

Q. And as a result of that meeting, did the National Cancer Institute agree to go forward and conduct clinical trials on Merck's cyclic compound EMD 121974?

A. Yes, they did.

[1554] * * *

Q. BY MR. WEIL: Based on your own understanding, was any of the work done by Dr. Cheresh, prior to the filing of the EPG, preclinical research?

A. Yes.

Q. And what research was that, sir?

A. It basically overlaps. I mean, the judgment — the judgment that you make, whether it's preclinical, is only after

you make the decision that the thing is going to the clinic. Then, by definition, the assays which have been performed, which are relevant — they are now included in the pre — in the clinical development program. They become significant bits of preclinical research. But the overlap between the basic, basic biology, which is what David was — we were funding David's lab to do, where it shades into an actual — please do this because the FDA need it, it's only clear afterwards. [1555] There is no — there is no direction at that stage, at these early stages, before the EPG was formed. The work should be done because it's fulfilling FDA requirements. It was there, because it was there. He was doing basic scientific research, which was subsequently, as relevant research, incorporated into a drug development program. The information couldn't be excluded.

Q. Well, let me call your attention back to Exhibit VV, which we looked at before lunch.

A. VV.

Q. Why wasn't — V like Victor.

A. Yes.

Q. If this was preclinical research, why wasn't any of it included here on this chart?

A. Well, that's what I was trying to convey with my answer. I think I said that there was — it was a computer error. So the problem is that — there is actually a personnel error. The project actually overlaps to the left of this chart. So I would cue 4 and so on, before this actual project schedule is put down there. It is just not — hasn't been included in

this chart. The Microsoft Access program — they didn't know it had to do — had a little truncated line to the left-hand side of the chart. It exists. There is other information which is feeding into this chart. It's just not included here.

* * *

[1558] * * *

We were talking about the work Dr. Cheresh did leading up to the decision that constituted the EPG for 85189. Why wasn't Dr. Cheresh made a member of that EPG?

A. Wasn't a member of Merck — independent researcher.

Q. And who, then, can be a member of an EPG?

A. It's purely among Merck, internal construct for putting the drug onto the market, basically. Only Merck internal personnel.

Q. Returning, then, to the question of organic compounds or mimetics that we were talking about earlier, are you aware of experiments performed by Dr. Cheresh prior to 1997 in which he compared mimetics to the accused compounds in this case?

A. I can't remember the precise dates at which the experiments took place, but certainly very, very early on in the functioning mimetic program David had done assays using such functional mimetics certainly.

Q. Was that program underway when you joined Merck in '93?

A. Yes, it was.

Q. What sorts of assays were being performed at that time in 1993 to evaluate the efficacy of mimetics as alpha-v-beta-3 inhibitors?

MR. BECKWITH: Object, Your Honor. I'm not sure if [1559] he's referring to Merck or Scripps.

THE COURT: Go ahead. Clarify.

Q. BY MR. WEIL: At Merck, when you joined Merck.

A. The assays were being done at Merck with Merck compounds and — excuse me. Can you refresh my memory of the question?

Q. What sorts of assays were being performed at Merck in that time frame?

A. Thank you. The same assays that were being performed with peptides, so receptor inhibition assays, followed by tests in cell adhesion when there are active, interesting active compounds.

Q. Would you take a look at document RP.

A. I have that document.

Q. Did you perform some of the work that's reflected here in RP?

A. It's a report of my laboratory, yes.

Q. I'm not asking about the document specifically. Do you recall that work as you sit here today?

A. Yes.

* * *

[1571] Q. BY MR. WEIL: Let me clarify my question. It was open to misinterpretation. When I say "give data," I meant in the course of your discussions on that day, when you met with Dr. Pluda, did you discuss data other than data for the 121974 compound?

A. Yes, we did.

Q. What other cyclic compounds, Merck cyclic compounds, did you discuss that day with Dr. Pluda?

MR. BECKWITH: Object, Your Honor, it's hearsay.

THE COURT: You may testify as to what the subject of the discussions were. Go ahead. You may answer that.

THE WITNESS: Yes, sir. We presented transparencies where we showed comparisons in the assays I've been describing between 85189 and 121974, and also the early compound, 66203. And I think there were one or two other compounds to show [1572] different activity profiles were possible.

Q. BY MR. WEIL: Was some of that data derived from the work of Dr. Cheresh?

A. I believe some of the data was from Dr. Cheresh, yes.

* * * *

APPENDIX 39 — TRIAL TESTIMONY: CROSS EXAMINATION OF SIMON L. GOODMAN, PH.D., DIRECTOR OF THE LABORATORY OF CELL ADHESION IN PRECLINICAL ONCOLOGY AT THE MERCK FACILITY IN DARMSTADT, CALLED BY DEFENDANTS ON FEBRUARY 25, 2000

[Commencing at page 1574]

Q. Yes. He's an employee at Merck?

A. He is, yes.

Q. Now, Dr. Schmitges has given some testimony in this case via a videotape presentation. I want to ask you about some of the things he said.

The question was put to him, perhaps you could explain for the record the difference between a research program and a development program. And Dr. Schmitges answered: Research programs — research program means that we try to identify compounds that have activity in this field whereas development means the testing of such compounds in animals to do toxicology studies and to test them in human beings.

My question to you, sir, is do you agree with that distinction drawn by Dr. Schmitges?

A. I don't agree with that, no. Dr. Schmitges has been outside the laboratory for rather a long time.

Q. What is Dr. Schmitges' position at Merck?

A. He's the head of Biological Research.

Q. And could you explain where that position is in relation to you in the Merck hierarchy?

A. He's the boss of my boss.

Q. Boss of your boss. And Dr. Schmitges has been with Merck for a very long time, hasn't he?

A. I don't know the exact details, but he's been there a long time, longer than I have, yes.

[1575] Q. And would you agree that Dr. Schmitges has a good understanding of the terminology and concepts that are used in Merck?

A. I would say his understanding is, to some extent, limited.

Q. Now, there has been — you just testified about a mimetics program that's being conducted at Merck.

A. Yes.

Q. The term "mimetics" is used with relation to RGD peptides on occasion, correct?

A. I don't agree with that, no.

Q. Now, you explained to the jury what you thought a mimetic was. Do you remember the lock and key, and RGD would be a key maybe, a brass key, whereas a mimetic might be a plastic key?

A. Yes.

Q. Is the idea of a mimetic that it mimics the RGD function?

A. It mimics the pocket in the receptor, not the RGD. It mimics the pocket in the receptor. We have no idea what the relationship is between — I mean the lock — that's the problem with the lock-and-the-key analogy, Mr. Flores. It's not true. I mean, the lock and key are concrete — sorry — brass. We have no idea what the receptor — the hole in the receptor looks like. It's just there. RGD-containing compounds work.

And so when you have a mimetic, it's a mimetic which fits [1576] in some hole in the receptor and does the same thing as RGD. That's why this interesting discussion about terminology — it is a functional organic mimetic, but what it's miming is the hole in the receptor. The receptor is blocked. We're not interested in RGD. We're interested in the receptor. That's what's blocked.

Q. Well, you're interested in something that has the same blocking function as the RGD, correct?

A. No, no, no. We're interested in blocking the receptor. We're not interested in RGD function. RGD just happens to do it. It's a hole — the receptor has got a hole of an undescribed sort of shape, which, yes, I mean, all of these extracellular matrix molecules with RGD and which we all know about, yes, they do fit, right. And RGD peptides, they do fit. But there is also all of this other stuff, these mimetics, which also fit, and they are totally different. I mean, if you crystallize them, they look different in crystal space. They are not the same structure as the RGD things. They are mimetics for the receptor. They are mimetic inhibitors of the receptor. That's why it's a functioning mimetic.

Q. So they are very different?

A. They are very different.

Q. But they both block?

[1583] * * *

Q. So when did Merck get the CAM assay in a functioning state for screening purposes?

A. The assay was available all the time, basically. I mean, it was — it was a case of we had the thing up and running and it was a case of putting more in there. But we didn't — the point — the point is that we never needed it for screening purposes. I mean, it was never used in Merck for screening purposes, so the question is misleading. That's why I'm sort of driving around it. We never used it for screening purposes because we were already there. We already had data from Dr. Cheresh's laboratory. We needed it just for, you know, the odd [1584] assay. It was never used in the screening.

Q. You didn't need it because Dr. Cheresh's laboratory was doing the screening, correct, with the chick CAM assay?

A. Dr. Cheresh —

MR. WEIL: Vague with respect to time, Your Honor.

THE COURT: Time?

Q. BY MR. FLORES: Prior to the date of your deposition testimony, which was November of 1998.

A. I believe Dr. Cheresh referred to this problem of the word "screening." So screening is a plastic word. So, for example, can I just — may I be allowed to give the example so that the jury will at least understand what's going on here? I mean, last year we did over five thousand receptor assays, over five thousand, five thousand compounds in receptor assays. So this is a screen. It's what we call, in the pharmaceutical industry, would be like a middle through-put screen. A high through-put screen would be hundreds of thousands. And a low through-put screen would be 10 or 50, somewhere around there. So "screen" is a plastic word. So when I said — when I'm saying — when you use the word "screening" at Cheresh's laboratory, Dr. Cheresh has never had more than, in his whole collaboration with Merck, has never tested more than some 50 compounds, I think.

Q. Well, I'm using or I meant to use the word "screening" in the same way that Dr. Sutter used it in Exhibit 500 when he [1585] said, "I suggest to keep the CAM assays in San Diego running by contract with the clause, as soon as they are successfully established in-house, the use for screening purposes in San Diego will be terminated." Let's use it in that sense.

A. Right. So Dr. Sutter is no longer aware of the situation when he's — when he suggests screening here. I mean, screening is defined here as being a few assays, five or ten assays. And those, as you are aware, from the '98 agreement, are those assays which were written into the contract

subsequently. That's the level of screening to what's being referred. Ten compounds per year, I think, is the thing which is written into the actual contract.

Q. So you don't agree with Dr. Sutter's use of the word "screening."

A. Well, I don't know in what sense he's using it here.

* * * *

APPENDIX 40 — TRIAL TESTIMONY: DIRECT EXAMINATION OF CHRIS A. STORGARD, M.D., PH.D., SENIOR RESEARCH ASSOCIATE AT THE SCRIPPS RESEARCH INSTITUTE AND FORMER FELLOW OF THE CHERESH LABORATORY, CALLED BY DEFENDANTS ON FEBRUARY 25, 2000

[Commencing at page 1590]

* * *

Q. Did you subsequently meet with Dr. Cheresh to discuss possibly doing research at his lab?

A. Yes. I approached Dr. Cheresh directly to see whether or not I could investigate the role of angiogenesis in rheumatic disease, namely, rheumatoid arthritis.

Q. And did you, in fact, then carry out a year of research in his lab?

A. That's correct.

Q. Now, did you design some experiments to conduct during that year?

A. Yes, we did.

Q. And just for the jury, what calendar year are we now talking about?

A. That would have been the calendar year of 1996 to '97 is when I formally began training there.

[1591] Q. Did anybody help you in designing the experiments for this year of research?

A. Yes. I was involved — I was working with Dr. David Cheresh as well as another Ph.D. in the lab, which is Dr. [STUBECK].

Q. Now, what model did you adopt for your experiments?

A. We used a model which has been around since the 1960s. It is the use of a rabbit arthritis model.

Q. Could you briefly describe how that works?

A. In this model we take rabbits and we inject into the, under the skin, a protein called ovalbumin, which is essentially the protein from egg white. And then we come back and we inject again three weeks later. At this point in time the rabbit has seen this protein as foreign and has made antibodies against it. So, essentially, we have immunized these rabbits against this protein.

And then we come a week later and we inject the same protein into the knee. So now the rabbit has antibodies recognizing this foreign protein, and so it forms an inflammatory response in the knee. And this inflammatory response can become chronic and resembles rheumatoid arthritis.

Q. Now, does this model that you adopted, does it simulate any sort of human disease?

A. Yes. As I mentioned, the value of this model is for its use in studying rheumatoid arthritis. And if I may expand

on [1592] that, its value is not in studying how rheumatoid arthritis begins, but the value of this model is that it is useful in studying potential drugs which will impact the arthritic disease. So drugs that have been effective in human disease are also effective in this model. Drugs that are ineffective in human disease are ineffective in this model. So we chose this model to study whether or not the drugs developed in Dr. David Cheresh's lab would potentially work on a model of human rheumatoid arthritis.

Q. And what did you find out during that first year of research?

A. During the first year of research we had some preliminary evidence to suggest that these compounds which inhibited angiogenesis would, in fact, decrease arthritis severity.

Q. So was that, then, the end of your research on angiogenesis and arthritis?

A. Actually that was essentially the beginning, because we had some initial positive results, and now these results needed to be expanded, reproduced, replicated.

Q. Well, was your fellowship over after that year of 1996?

A. The fellowship ended in 1997.

Q. Excuse me, in 1997. Did you then continue your research?

A. Yes, I did.

Q. And where did you continue your research?

A. In the lab of Dr. David Cheresh.

[1593] Q. All right. Now, I'd like, then, to talk with you a little bit about the research that you conducted during the year 1997. All right?

Some of the experiments that you conducted during that year are accused of infringement in this case. Are you aware of that?

A. Now I am, yes.

Q. Okay. And they have been given the name, for purposes of this lawsuit, rabbit arthritis.

A. Okay.

Q. Could you just, again, briefly tell us what were the experiments that you were conducting during the calendar year 1997 with respect to rabbits?

A. Well, what we were doing at that time is we were seeing whether or not these compounds could, in fact, reduce arthritis severity. So the exact experiments of what we had done at that time were, we would induce arthritis in a group of rabbits. We would take those rabbits and we would not treat a certain number of rabbits, we would treat a rabbit with a control compound, and we would treat a rabbit — meaning a compound that should not have any effect — and we would treat the rabbit with the compounds, the active antiangiogenic compounds. And we started — initially it was treating very early in the disease, essentially 24 hours after the disease started. And then we looked and seen whether or not we had an [1594] impact on arthritic disease.

Q. Now, in your answer you mentioned "these compounds." What compounds were you talking about?

A. We used a number of compounds. We used — I believe the number is 66601. I know it ends in 601. Compound 203, and we also used the compound 189.

Q. Is it possible you used 85189?

A. Yes, that's the number.

Q. 66203?

A. That's correct.

Q. And 69601?

A. Yes.

Q. Now, why — strike that. Let me first ask you, what were you trying to find out with this series of experiments you did in 1997?

A. Initially the very first question that we had was whether or not, if we could inhibit angiogenesis, could we somehow impact arthritis severity. And so, in order to do that, we used the compounds of 66203, which was the active antiangiogenic compound, and we had to compare it to a control drug, which is 6 — 69601, which did not have any effect on angiogenesis. So we wanted to first find out whether or not one drug would work over another.

Q. Once you found something out about whether the cyclic peptides would work, did you do any other experiments during [1595] 1997 to find out anything else?

A. Yes, we did.

Q. What did you do?

A. We compared the compounds — sorry, I forget the first number — 203 to 189. If I can just use those numbers, it would be easier for myself. So we compared compound 203 to compound 189. The reason for doing that is that it had previously been discovered in the lab that there are two integrin pathways that play a role in angiogenesis — integrin alpha-v-beta-3, which was preferentially targeted by the peptide 203, and compound 189, which targets another integrin, alpha-v-beta-5.

Q. Now, did any of the experiments you conducted during 1997 shed any light on pharmacology or pharmacokinetics?

MR. BECKWITH: Objection, Your Honor. I don't know that the witness has been established as an expert in those particular areas.

THE COURT: Go ahead.

MS. THAYER: Well, the witness — let me see if I can, without using those words, just let the witness talk about what he found and what he was looking for.

THE COURT: Very well.

MS. THAYER: Would that be all right? All right.

Q. BY MS. THAYER: With respect either to the length of time of the drug being in the bloodstream or the way in which these [1596] drug candidates work, were any of your experiments designed to shed light on those issues?

A. Yes. There was one group of experiments where we took a look at a fluorescent labeled compound. So this compound, if you look under a microscope, you could see that it was actually there. The way we were delivering these drugs was direct injection into the knee. And the question was, well, how long are those drugs there and where do those drugs actually go.

So what we did is we took this fluorescent compound, which was similar to the compound 203, the active drug, we injected it into the knee of an arthritic rabbit. Came back 24 hours later and looked to see where that drug was. And the rationale for that was, one, to find out, do we still have drug in the joint, to see how long that drug sticks around, and, also, where does that drug go, does it target — well, does it seem to go to the blood vessels, as we think it should.

Q. Did any of your experiments during that year of 1997 shed any light on toxicity or nontoxicity?

A. Yes, they did. We also wanted to make sure that, if we could somehow impact inflammation or arthritis severity, that we weren't doing it by reducing the number of inflammatory cells. Many of the drugs used in arthritis today are targeting the immune system, and they often — some of the drugs can lower your immunity by decreasing the bone marrow's ability to produce those drugs. So what we did is we looked to see [1997] whether or not we lowered — whether or not there was any side effects of what we could see in the blood. Essentially what we did is we did what was called a peripheral blood count. So it is the same kind of thing as when you go in and you get your blood drawn

and they look at how many red blood cells are there, how many white blood cells are there, how many platelets are there. And so we drew blood from these rabbits before administration, during administration, and then at the end of the study to see whether or not there was any decrease in any of the cell count, to see whether there was any toxicity related with this drug.

Q. Now, did your experiments during 1997 show you anything about which of the cyclic compounds were more effective?

A. Yes, they did.

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APPENDIX 41 — TRIAL TESTIMONY: DIRECT EXAMINATION OF JAN SOMBROEK, PH.D., MEMBER OF MERCK'S BOARD OF DIRECTORS, CALLED BY DEFENDANTS ON FEBRUARY 28, 2000

[Commencing at page 1673]

* * *

Q. And so what is the purpose of preclinical tests?

A. The purpose is to generate interesting projects for the pipeline and to generate interesting projects for clinical development.

Q. And what do these tests show that will help you identify interesting candidates for the pipeline and for clinical development?

[1674] A. We have to show that these projects are superior in terms of efficacy and safety.

Q. And when you say that these projects are superior, does that necessarily entail some comparative testing between different products or, excuse me, different compounds?

A. That is correct.

Q. We have heard some testimony last week about development projects. Is preclinical research conducted at all during the time before a development product is formally initiated?

A. Could you please repeat that?

THE INTERPRETER: It was very long, says the witness.

(Question read by the interpreter.)

THE WITNESS: Yes.

Q. BY MR. ROOKLIDGE: So whether an activity is preclinical research depends on the nature of that research itself, not whether a development product has been formally initiated?

MR. FLORES: Objection, leading.

THE COURT:. I'm going to allow it. It's a preliminary question.

THE WITNESS:. That is correct.

Q. BY MR. ROOKLIDGE: So the nature of that preclinical research is devoted to the efficacy, the safety, and the comparative analysis of the compounds.

A. That is correct.

Q. Now, several days ago, by videotape, Dr. Schmitges [1675] testified about his perception of the distinction between research and development. If I could read that short bit of testimony to you, I'd like to ask you if you agree with Dr. Schmitges' view of that distinction.

Dr. Schmitges was asked: Perhaps you should explain for the record the difference between the research program and the development program.

And he answered: Research program means that we try to identify compounds that have activity in this field, whereas development means the testing of such compounds in animals to do toxicology studies and to test them in human beings.

And he was also asked: Development projects are focused on regulatory requirements; is that correct?

And he answered: Yes, this is primarily toxicology and testing in human, in trials in humans.

And then he was asked: And research programs are not oriented to regulatory requirements?

And then he answered: Not at all, no. They are much more proximal. It's the start of a project.

Do you agree with Dr. Schmitges about the distinction between research and development?

A. Basically, yes.

Q. Now, is this distinction a clear-cut distinction?

A. No.

Q. Why not?

[1676] A. During the tests of these projects, we can sometimes find the tests that are relevant to research at the beginning also become relevant for development.

* * * *

APPENDIX 42 — TRIAL TESTIMONY: DIRECT EXAMINATION OF MARTIN FRIEDLANDER, M.D., PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE AND FORMER RESEARCH COLLABORATOR WITH DAVID A. CHERESH, CALLED BY PLAINTIFFS ON FEBRUARY 29, 2000

[Commencing at page 1831]

* * *

Q. Now, what were the general categories of experiments that you used Merck cyclic RGD peptides in?

[1832] A. The general categories would be called efficacy, and that is to test whether or not a given drug could achieve a given effect in an animal. In my case we were working largely with animal systems. The other area is what we call broadly pharmacokinetics, and that is to see how the potential drug would behave in a living system, how it's metabolized, how it's excreted, how much actually winds up where you think it will wind up. I think that's a fair statement of the general categories we worked with.

We were also interested in trying to understand something about mechanism. So if we could, we tried to design experiments which would give us some insight into mechanisms as well.

Q. Apparently my question was not specific enough. What were the specific types of experiments that you used? By that I mean, did you use these peptides with any particular animals?

A. You had asked about categories. Isn't that what you said?

Q. Right. But what I want to identify is the categories of experiments.

A. So the types of animal experiments? Categories I gave you already. You want something different now.

Q. The categories of experiments, not what you were attempting to learn, but rather the category of experiments you actually performed.

[1833] A. I don't mean to seem argumentative, but it seems — it's semantic. Categories of experiments to me mean what you're directing — trying to do in the experiments.

Q. No. No. I want to know what you did, not what you were trying to learn. For example, did you do rabbit cornea assays?

A. Yes, we did.

Q. Okay. Did you do experiments with mice?

A. Yes, we did.

Q. What kind of experiments, general category of experiments, did you do with mice?

A. Types of experiments we did to address the issues I've just gone over, would have involved basically two models which were under use in my laboratory. One involves stimulating new blood vessel growth in rabbit corneas. The cornea is the clear dome covering the front part of your eye. And the reason we like to use that model is because the cornea is ordinarily a vascular — ordinarily does not have the blood vessels — does not have blood vessels in it. So we would

put a chemical in to stimulate the growth of new blood vessels and ask the question: how can we modulate the animal's response to that.

The other types of experiments we did involved using a mouse retinal model. And the retina is like — if you think of your eye as a camera, the retina is like a film in the back of the camera. The retina, in fact, is the site where most [1834] abnormal new blood vessels grow in certain types of blinding diseases, most of which I see — which is what I spend most of my time doing in the clinic. And so the thought was, if we had an animal model which would most closely approximate what happened in patients, we could better understand and evaluate these compounds.

So, in summary, the two basic types of experiments we used were the rabbit corneal model, where we made new blood vessels grow, and the mouse retinal model, in which new blood vessels grow by a natural process and we would attempt to interfere with that using a variety of compounds.

Q. And some of the compounds you used were the cyclic Merck RGD peptides?

A. That's correct.

Q. 662 — EMD 66203 was one of those compounds?

A. Yes, it was.

Q. Now, do you remember using EMD 85189?

A. Yes, I do.

Q. And do you recall that that had the structure cyclo RGDDV N-methyl valine?

A. Something close to that, yes.

Q. And do you remember using EMD 121974 in that model?

A. Yes, I do.

* * *

[1838] * * *

Q. Did you ever review, in connection with your educating yourself about cell adhesion, did you ever review a publication by a Mr. or Dr. Hayman involving detachment of cells using soluble RGD peptide?

A. No, I've never — actually never heard of a Dr. Hayman.

Q. How about — perhaps if I told you the name — the other authors are Drs. Pierschbacher and Ruoslahti. Did you ever review any of their publications that specifically dealt with detaching preattached cells using a soluble RGD peptide?

A. I've read thousands of papers. I'm sure — I may — I'm sure I've read some papers of Dr. Ruoslahti and Dr. Pierschbacher. But with regard to specific contents you're talking about, I never — I did not.

Q. Dr. Friedlander, I'm going to show you what's been marked Plaintiffs' Exhibit 406. Is that your signature on page 6 of Plaintiffs' Exhibit 406?

A. Yes, it is.

Q. And were you the principal investigator primarily responsible for this grant request?

A. Yes, I was.

Q. And please tell the jury what Exhibit 406 is.

A. This is an application that I submitted to the Lions Sightfirst Diabetic Retinopathy Research Program of the American Diabetes Association, the funding of some of our [1839] research in our laboratory, submitted in January of 1995.

Q. Now, on the first page of Exhibit 406, there is a reference to Kaye Wynne. Who is Kaye Wynne?

A. Kay Wynne is a Director of Research and Contract — Grants and Contracts. She's got a different title now, but at the time she was called Director of Grants and Contracts at the Scripps Research Institute.

Q. Was her signature required on this grant application?

MS. THAYER: Objection, vague, calls for speculation.

THE COURT: Well, do you know? Do you have knowledge?

THE WITNESS: Well, I have knowledge that — it's customary and usual, is that the language, for a — let me finish — for a representative, a legal representative, of the Institution to appear on every grant application. Some representative of the Institution must be on every grant application we make. Whether Kay was significantly required in this case, I wouldn't have any idea.

Q. BY MR. BECKWITH: Now on page 6, I believe you said that's your signature there?

A. That's correct.

Q. And you signed it around January 31st of 1995?

A. That's what the dates would imply, yes.

Q. And under Approved Head of Department, do you recognize that signature?

[1840] A. Yes, I do.

Q. Who is that?

A. That's Bertie or Norton B. Gilula, chairman of my department in cell biology.

Q. And also an employee at Scripps?

A. Yes.

Q. And was it customary to get the head of the department to sign off on grant applications as well?

A. They sign off at various points in the process, and different granting agencies have different requirements as to who signs these documents.

Q. Now, I'd like to direct your attention to page 10 under the heading "Introduction." And I want to specifically refer you to the section that begins, "In order to proceed to Phase I clinical trials, a rigorous series of preclinical testing is necessary and must conform to good laboratory practices (GLP) standards. The funds requested in this application are to purchase equipment and hire personnel specifically for the purposes of completing the necessary preclinical toxicology, pharmacokinetic and bioassay experiments." You wrote that, didn't you?

A. Yes, I did.

Q. And at the time that you wrote it, your laboratory did not comply with GLP standards.

A. That's a fair statement.

[1841] Q. And the experiments that you did with the rabbit cornea assay did not conform with GLP standards, correct?

A. You're referring to the experiments, the preliminary data, or the experiments we were proposing to do here?

Q. No, the experiments that you had done up to that point.

A. That's correct. Had not been done to GLP standards.

Q. And the experiments that you had also done with the mice retina, those also did not comply with GLP standards.

A. That's correct.

Q. And you also did, I think you said, mice retinal vascular — maybe you can help me out there.

A. Mice retinal vasculogenesis models.

Q. Thank you. Those experiments also did not comply with GLP standards?

MS. THAYER: Objection. Vague as to what period of time counsel is talking about here.

THE COURT: Go ahead and establish the time.

Q. BY MR. BECKWITH: At some point in time did your laboratory become a GLP certified laboratory?

A. No, we did not.

Q. So it doesn't matter what period of time we're talking about. The experiments done in your lab did not comply with GLP standards; is that right?

A. That's a fair statement.

* * *

[1843] * * *

Q. Does that refresh your recollection that you didn't get the EMD 121974 in with the GMP quality?

A. Well, again, I'd like to look at the correspondence, because I know I requested it and I remember that it was an issue at the time, which is exactly what I stated in the deposition. There was an issue about availability because they were starting clinical trials. Whether, in fact, we got material after that that was GMP quality, I honestly don't recall. But I am sure we can find out from records.

Q. Do you recall if the EMD 66203 that you were using prior to 1997 was of GMP quality?

A. Probably not, only because it was not the candidate that [1844] actually went to the patients, so I would be surprised if Merck had manufactured to GMP standards.

Q. At some point in time you learned that a lawsuit had been filed in connection with the use of Merck's RGD peptides at Scripps?

A. Yes, that's correct.

Q. Did you change in any manner the way in which you were carrying out your experiments after you learned that the lawsuit was filed?

A. No, I didn't.

* * * *

APPENDIX 43 — TRIAL TESTIMONY: CROSS EXAMINATION OF MARTIN FRIEDLANDER, M.D., PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE AND FORMER RESEARCH COLLABORATOR OF DEFENDANT DAVID A. CHERESH, CALLED BY PLAINTIFFS ON FEBRUARY 29, 2000

[Commencing at page 1851] * * *

Q. Now, you just mentioned that your research was published in Science. Do you consider that the experiments that you ran that underlie this article were preclinical experiments or basic research or both or neither?

A. Well, it's very difficult to get a clinical study published in Science. I think you have to have good, solid, basic science, and what makes it even more exciting is if it has clinical relevance. This work, I think, had both. It was excellent basic science and then it had very clear clinical application.

Q. Well, how can something be basic science and yet have relevance to a clinical application?

A. I guess it's a little bit like me. I mean, you know, we do basic science in the laboratory, but we often think about what we're doing in the laboratory and potential application to patients. So, for example, if you could put a drug into a patient, you darn well better know a lot about what the potential side effects of that drug are and how effective that drug is before you go ahead and do that. And the best way to avoid significant problems after you put something into a patient is to have as much basic science, fundamental

understandings about that drug before you put it into a patient. Yes, did you have a question?

* * *

[1855] Q. Now, I'd like to go and ask you some very specific questions about the experiments conducted in your laboratory from 1995 through 1998. First of all, though, we already established that you had something to do with the 1995 Merck-Scripps agreement, Exhibit 46. Do you recall that?

A. Yes, I do.

Q. All right. Before that agreement was entered into, did you have any role in laying out the proposal that was made to Merck that led to this agreement?

A. Yes, I did.

Q. Would you look at tab TD in your book and tell us what that is?

A. This is a copy of a funding proposal entitled, "Scripps/E. Merck Program on Angiogenesis, Principal Investigator, David A Cheresh."

Q. And what is the date of this document?

A. February 1, 1995.

Q. And who prepared this document?

A. Dr. Cheresh prepared it with input from myself and, I believe, several other co-investigators.

Q. And what was done with this document?

A. This was used, was sent to Merck and given to the [1856] appropriate people there, to see if they would be interested in funding this program.

Q. Now, could you turn to the page that's marked Bates number S-31405?

A. Yes.

Q. What is that?

A. This is a letter of intent to collaborate and commitment to this project sent from me to Dr. Cheresh.

Q. And why did you send this letter to Dr. Cheresh?

A. Well, it's usual, it's customary, when individuals are proposing to collaborate with one another, to include a letter stating this intent to collaborate along with the research proposal.

Q. And did you state in this letter anything about the basis for your interest in the collaboration?

A. Yes, I did.

Q. Can you look at the third sentence in the letter?

A. Beginning with "not only"? Yes.

Q. Yes. Could you read that?

A. "Not only does this represent an exciting area of overlap, with my interest in integral membrane proteins and the regulation

of cell-cell interactions, but it also provides a novel approach to designing and implementing therapeutics directed against diseases of neovascularization."

Q. What did you mean by that sentence?

[1857] A. What I meant was, basically what I stated several minutes ago, that this was the first publication, the first evidence, that is the work that came from Dr. Cheresh's laboratory, that convinced me that there was actually a potential drug out there which provided a rational basis for, you know, for treating diseases of neovascularization, and I thought it was tremendously exciting.

Q. Now, in the early part of 1995, did you propose to Merck a series of preclinical studies to be performed in your laboratory?

A. I was involved in putting together a proposal in which part of that proposal was to help Merck with their preclinical development program as well as to continue to do basic science.

Q. And what specifically did you propose to Merck that you would do during the period of funding?

A. Would you mind if I — my general recollection was that we offered to use these models which I've discussed earlier to test some of the compounds which they were interested in moving into clinical trials. Is that the part of the document you're referring to?

* * *

[1862] * * *

Q. During the period from 1995 through 1998, did you perform or supervise preclinical experiments that were designed to obtain data for use with regulatory authorities?

MR. BECKWITH: Objection, Your Honor, lacks foundation. Witness hasn't been identified as an expert in the area of FDA requirements.

THE COURT: He may testify as to what experiments he conducted and precisely what they were for.

Q. BY MS. THAYER: Do you have the question in mind?

A. Yes. Yes, we did.

Q. And I'd like you to focus on the types of experiments that have been accused of infringement in this case. And I have [1863] included those in your binder in case you need to refer to them.

Let me first ask you, though, you've already been asked some questions about the rabbit and the mice types of experiments. Why did you decide to conduct those types of experiments during this preclinical phase?

A. Well, there are a number of reasons. Again, a general background, I also serve as a principal investigator on several clinical trials in the clinic, unrelated to this. I know, as a principal investigator, on a clinical trial, there is something called an investigator's brochure that's given out. So I have some familiarity with what kind of background material one

wants to have as a clinician in terms of, you know, feeling comfortable using certain drugs in clinical trials. I also have learned through a number of conversations with people at the FDA and other colleagues involved in clinical trials what sort of preclinical data is probably important for, you know, for taking this to regulatory agencies.

With that in mind, I felt that what was important was efficacy, that is, will this drug really do what we want it to do, okay. Number two, safety, that if it does, will this be safe in treating patients. If you kill a patient in the course of making them see again, the drug is really not very successful. And those are the guiding principles in terms of designing some of these preclinical experiments.

[1864] Q. All right. Let's focus specifically on the rabbit corneal assays. I believe you've already described what that assay is, but could you just again briefly, very briefly, say what it is that you do in a typical rabbit cornea assay.

A. When a rabbit — in this rabbit model I mentioned, the cornea, this clear dome over the front of the eye, is ordinarily without blood vessels. We put a little pellet into the eye which contains chemicals that stimulates new blood vessel growth. This is done under sterile conditions in an operating room in a fashion similar to how we would operate on a human eye.

We then ask the question, can we administer drugs, such as cyclic RGD peptide antagonists, to the animal in a fashion analogous to what we would do to the human to inhibit the growth of these new blood vessels.

So, for example, in the antibody studies we have done, we administer the antibody locally, by surgically implanting it into the pellet. We would not ordinarily do that in a human. We would not take someone into the operating room and put a pellet into their cornea, but rather we prefer to give them a pill or an injection. So these efficacy studies in the rabbits were done with drugs, the 121974 and other peptides, to see if we could subcutaneously administer this and have the desired effect in the eye.

Q. For those of us who are lay people, what's subcutaneous?

[1865] A. Oh, I'm sorry. It's under the skin or — intramuscular is into the muscle or under the skin. Much in the way, if you have had a TB test, they stick a little needle under your skin and inject something.

Q. You mentioned that you tested more than one of the cyclic peptides in this assay. Why is that?

A. Well, again, you never really know what the best drug is going to be unless you have something to compare it to. And, in fact, quite often, when we start clinical trials, we wind up using a different drug down the road. So it is very important to start off with what you have in hand at the time and continue to use that as a basis of comparison for subsequent modifications in those drugs that come along.

Q. All right. Let me ask you also, did the rabbit cornea assays provide any data concerning how long — where the drug goes in the animal or how long it stays in the bloodstream?

A. Absolutely. Those are the pharmacokinetic studies. So, in addition, once we saw efficacy, that is, we were able to prevent new blood vessel growth in rabbit corneas by administering these peptides subcutaneously or systemically, the next question was how much gets to where we want it. And, again, if you think about it, if you inject something systemically, it goes through your whole circulation. The eye only counts for a very small part of that circulation. So a meaningful question is, how much do you have to give [1866] systemically to get it in therapeutically meaningful values into the eye.

So we could take, for example, radiolabel compounds, compounds which have a radiolabel tag on it, inject it systemically and ask how much actually gets into the eye. And those are some of the types of experiments we did.

Q. I think of a radio as something I turn on and listen to music. What do you mean by radiolabeling?

A. That is a radio, but — these are radioisotopes, sorry. So, for example, something called — something which is radioactive. That's common. We do this in patients also in terms of looking at thyroid activity, I-125, to a patient to see how their thyroid works. The same principle in animals.

Q. Finally, when you say you put this radioactive tag on the drug candidate, why does that help you see where it goes?

A. What we can do, we can inject it under the skin and then take samples at various time points of the back of the eye and ask the question, does the radioactivity wind up in the eye. We can also measure, for example, urine, and we

can see how much is urinated out, how much winds up in the feces, how much winds up in different parts of the body. So it's a fairly standard way of determining the distribution of a drug once you inject it into a patient or an animal.

Q. All right. Let's turn to the fourth type of experiment that's accused of infringement here, the murine retinal [1867] vasculogenesis. Let me first ask you, is that term "vasculogenesis" somewhat of a misnomer?

A. At this point in time I'd say, yes.

Q. Okay. And, remember, you're talking slowly now. Could you explain why that is?

A. At the time we started out doing these experiments, the thinking was that — let me back up a little bit. When we're all inside the womb and we're in the last three months of development, your retinas do not have a blood supply. That retinal blood supply is formed during the last three months of gestation. A mouse is a little different. A mouse is born, okay, and then forms a retinal blood supply. So in many ways a mouse, during the first two weeks of its life, is analogous to a third trimester human. So we develop almost entirely in utero where mice and other types of rodents develop outside the mother's womb.

The thinking was that these blood vessels in the retina form as a result of a process called vasculogenesis. Vasculogenesis is defined as the de novo or the new formation of blood vessels from pre-existing cells. So the implication there are precursor cells sprinkled along the surface of the retina, somehow these magically coalesce and form blood

vessels. That was the thinking then. We now know this is probably not correct based upon work that we've been doing in my laboratory the last couple of years.

[1868] What really happens is these blood vessels come out of the optic nerve, which is the connection between the eye and the brain. And these blood vessel cells know where to go and they start pouring out over the retina, they form the retinal vasculature, during those first two weeks postnatally. So it may seem like a trivial point if you're not in the field, but it is very important because there are two different processes — there is such a thing as vasculogenesis and something that's angiogenesis. And many of the disease processes we see in eyes, for example, are the result of angiogenesis. So it is very important to establish in our field that, in fact, the models we're using really relate to angiogenesis and not some developmental event that occurs in the uterus or in utero.

Q. Now, referring back to the categories that you mentioned earlier about efficacy, safety, method of administration, that sort of thing, what, if anything, were these particular types of experiments designed to provide information about?

A. Well, as you hopefully remember from what seems like hours ago, we talked about what diseases really blind people, and it is not corneal neovascularization. There are diseases that result in corneal neovascularization, blindness, but most diseases blind patients from retinal neovascularization. So we felt it was very important to demonstrate efficacy, that is, to show effectiveness of these compounds in a disease which, as [1869] closely as possible,

approximates the real thing in people, and had to go looking for a model of retinal angiogenesis. And that's why we turned to this mouse retinal vasculo/angiogenesis model.

Q. Did you use more than one of Merck's cyclic compounds in this particular assay?

A. Yes, we did.

Q. Why did you do that?

A. Once again, it's very important you start out with one compound and, as new generations of the drugs come along, you need to compare it to previous compounds to make sure that it, you know, better, is it worse, is it the same, is it different.

Q. Did anything about this assay teach you about either the method of administration or the length of time that the drug candidate remained in the blood?

A. Yeah, we actually learned a lot from this assay. We learned several things. One is that you could, in fact, administer it systemically, that is, under the skin — we administered along the back — enough winds up in the eye to completely shut down the development of these new blood vessels.

Furthermore, if you do this — there are several aspects, I don't want to get too technical on you, but one aspect of this assay is, not only do we completely prevent the growth of [1870] blood vessels at all, but if you wait for eight days, a very curious thing happens in the mouse retina. The vessels have gone out along the surface during the first eight days.

Between day 8 and day 12, what happens is, these vessels then turn, dive a distance into the retina and form a secondary network, and, again, identical to what happens in human fetuses during the last trimester of life.

Interestingly, if you apply these peptides between day 8 and day 12, when the secondary, deep network is formed, so the primary network is already formed, but the deep network is forming, we completely shut down the new network without in any way whatsoever affecting the already established vessels. We were very excited about this because it shows, not only is it efficacious, but it's safe. That means the vessels that are already there — you got a newborn, tiny little mouse, these vessels are perfect, completely unaffected.

Q. All right. Again, let's keep it slow. We have one more category here. Mice retina, IF. What was that assay? Just what is it that you did? And then we'll talk about what you learned from it.

A. Okay. Again, that pertains to pharmacokinetics. What we're interested in here is, it's nice to inject something under the skin over here. It's nice to see an effect over here. But you feel a lot better if you actually see the drug you injected where you think it's going.

[1871] So, again, another little trick that the chemists at Merck can do is they can conjugate or they can attach their peptides to a molecule that glows in the dark, something called —

THE REPORTER: Do we have the spelling for that somewhere?

Q. BY MS. THAYER: Can you slow down and spell isothio — whatever you said.

A. Fluorescein, F L U O R E S C E I N. Isothiocyanate, I S O T H I O C Y A N A T E.

So you can hook together the peptide and the fluorescein. This will then glow. In the right light conditions this will glow. So we can inject that under the skin, wait for it to go around, then look at the eyes and ask the question: Is there something glowing in the eyes? And, more specifically, is something glowing where the new blood vessels are. And that's why we did those experiments.

Q. And what did you learn from those experiments?

A. Well, unfortunately — well, we learned — unfortunately, we learned that perhaps the glowingness was not quite bright enough to see everything we wanted to. But we also at the same time did manage to detect some glowing materials at the tips of those new blood vessels. So, as many things in science, not an unequivocal answer, but something which was very subjective.

Q. All right. Now, at some point in time were you asked to summarize your data in the form of reports?

[1872] A. Yes, I was.

Q. Could you turn to Exhibits XF and YC, and just first identify for the record what those are, first with XF?

A. XF is entitled "Report 6." It's a report prepared by a company called Theradex. And it purports — do you want me to read the title, too?

Q. No, you don't need — just, in general, what is it?

A. Generally it's a report prepared by a company which purports to summarize results of experiments done in my laboratory that pertain to the effects of Merck peptides on the murine retinal vascular/angiogenesis model.

Q. And for this report what particular Merck compounds are at issue?

A. EMD 66203 and EMD 85189.

Q. And what is Exhibit YC?

A. It's another report, Report 5, once again prepared by Theradex, which purports to demonstrate the effects of certain Merck integrin cyclic peptide antagonists and antibodies on the effects of angiogenesis in the rabbit corneal model.

Q. Now, how is it that Theradex had data from your laboratory in order to prepare this report?

A. Well, my understanding is that Merck retained this company to prepare these reports in preparation for IND filing and that we were asked to cooperate with this group where they came to our laboratory to look at our data to provide them with the [1873] data to prepare these reports.

Q. At some point in time did you get drafts of reports prepared by Theradex?

A. Yes, we did.

Q. Were there any errors in them?

A. Yeah, there were lots of errors.

Q. What did you do?

A. We completely rewrote the reports.

Q. Why did you do that?

A. I felt it was important that these reports be as accurate as possible.

Q. Now, since 1995 have you had any contact with FDA representatives concerning this proposed treatment for eye diseases?

A. Yes, I have.

Q. With whom specifically have you had conversations?

A. One individual who I've had at least two conversations with is Dr. Wiley Chambers.

Q. Just generally, what subjects have you discussed with Dr. Chambers?

A. I discussed the regulatory requirements by the FDA for putting a drug into clinical trials for ophthalmic indication, and I've also discussed a class of compounds, these integrin antagonists, and their potential use in treating ophthalmic disease.

[1874] Q. By the way, who is Dr. Chambers?

A. Well, at the time I believe he was the Director of the Division of the FDA which dealt with analgesics, anti-inflammatories, and ophthalmic agents.

Q. And did you contact him? Did he contact you? How did that come about?

A. I contacted him.

Q. Why did you do that?

A. Because he's the man. He was the one who basically supervised and was responsible for all ophthalmic therapeutics at the FDA.

Q. Approximately when did you have these conversations with Dr. Chambers?

A. In 1996, in the fall of 1996.

Q. Now, did you take into consideration your conversations with Dr. Chambers in any of your subsequent studies?

A. Yes, I did.

Q. Now, after your conversations with Dr. Chambers, did you prepare a pre-IND report?

A. Yes, I did.

Q. Would you look in your binder at Exhibit 62? Can you tell us what that is?

A. The pictures?

Q. No, no, just what the exhibit is.

A. The exhibit is entitled, "The Role of VNR Integrins in [1875] Ocular Angiogenesis."

Q. Slow down, please.

A. "The Role of VNR Integrins in Ocular Angiogenesis." And is a report prepared by myself and my colleagues reflecting the data we have accumulated concerning the use of particular antagonists and their usefulness in filing an IND.

Q. What did you do with this report?

A. I presented this to the appropriate individuals at Merck.

* * *

[1877] * * *

Q. BY MS. THAYER: Let me, then, ask you to turn to Exhibit 406. It's one of the exhibits that Mr. Beckwith gave to you.

Before we get to the paragraph that you've already testified about, let me first ask you about the introduction, which is at, I believe it's page 10.

A. Yes.

Q. And in the first paragraph did you state for this agency what your purpose or goal was in undertaking the proposed research?

A. Yes, we did.

Q. And was one of those goals or actually was the ultimate goal to enter Phase I clinical trials with a humanized form of this antibody?

A. That's what we hoped to achieve.

Q. All right. Now, you were also asked some questions about the last — excuse me — third paragraph, last sentence. Do [1878] you recall that, about GLP?

A. Oh, yes. Next to the last sentence.

Q. Right. Subsequent to your preparation of this document, in January of 1995, did you come to learn anything about the accuracy of the sentence, two sentences, that you had written right there?

A. To my embarrassment, yes.

Q. What did you learn?

A. I learned that you did not need to do GLP standard, you know — to do experiments at GLP standards in order to have them acceptable to the FDA as preclinical data.

Q. After you learned — well, let me first ask you, how did you learn about this mistake that you had made in this document?

MR. BECKWITH: Objection, Your Honor, calls for hearsay.

THE COURT: You may testify as to how he learned of it. You're not going to go into the document itself, but — it will be admitted only for the basis of how he learned. You may have that part of it.

THE WITNESS: Shall I answer the question? Yes?

Q. BY MS. THAYER: You may proceed.

THE COURT: Yes, you may.

Q. BY MS. THAYER: All right. Do you need the question read back?

[1879] A. No. I learned about it through conversations with officials at the FDA and with people who work in the pharmaceutical industry who had far greater familiarity, more experience than I did at the time.

Q. Did you, in fact, change your laboratory after January of 1994 to turn it into a good laboratory practices laboratory?

A. No. There was no reason to.

Q. And why is that?

A. Because, once again, one apparently did not need to go through the extraordinary expense and effort to do GLP quality experiments to have material accepted by the FDA to proceed with the clinical trial.

Q. So did you mislead this agency into giving you money for GLP experiments and then not conducting them?

A. No. We did experiments. This often happens, when you write a grant proposal, sometimes the course of those experiments change. And, in fact, I just had another recent NIH grant which turns out, for a variety of reasons, we couldn't do what we initially proposed to do. So you need to inform them at the appropriate time, tell them what you are

doing, and, if there are objections, they will let you know about that.

Q. Did you hide from the Lions Sightfirst Diabetic Retinopathy Research Program the fact that you were not going to do GLP studies?

[1880] A. No, of course not.

* * *

[1883] I also, in an effort to move ahead with the ophthalmic clinical trials, I spend a lot of times speaking with ophthalmic pharmaceutical companies in the hope that Merck would find someone they could collaborate with in terms of bringing this to the patient in terms of ophthalmic clinical trials.

Q. Let me stop you right there. You're talking about meeting with ophthalmic partners. Is that work that you were doing under the October 1995 agreement, consulting agreement, or under the second consulting agreement?

A. No, I'm sorry. I meant both, in general. That's more related to the work I do as a clinical consultant. That is a later clinical consulting agreement.

Q. Let's focus on that later one. I think you testified that you get something like $12,000 a year. Could you tell the jury what you do or have been doing in connection with that consulting project?

A. Well, again, I do things that are more clinically related, that is, these are specifically directed at trying to

bring these drugs into the clinic for ophthalmic indications, diseases like diabetic retinopathy and macular degeneration. And, again, I organize round-table discussions of similar to the one I already told you about that took place in Boston. I go to clinical facilities and talk with individuals about the [1884] ongoing research and what potential impact this would have. But probably most relevant, directly relevant, to that specific consulting agreement is I am working with Merck people in preclinical development, basic science, clinical development, and business development to find a suitable ophthalmic pharmaceutical partner to bring these drugs into the clinic for ophthalmic applications.

Q. Are there specific companies that you have been working with in the United States with respect to finding this partner for Merck?

A. Yes, there are, because the largest ophthalmic pharmaceutical companies in the world are located in the United States.

* * * *

APPENDIX 44 — TRIAL TESTIMONY: DIRECT EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY DEFENDANTS ON MARCH 1, 2000

[Commencing at page 2029]

Q. What do you mean by "regress"?

A. The tumor actually became necrotic, died, disappeared. In fact, became even smaller than our original tumor fragment that we put on. And this was quite a surprise to us and, I think, people in the field in general. And we published this work in the Cell paper in '94 that we've heard about.

Q. Did you do this research with any compound other than LM609?

A. Yes. At this stage we wanted to make sure that it wasn't just a property of the antibody per se, but it was really a property of inhibiting the receptor alpha-v-beta-3. So we chose to use the cyclic RGD peptide.

Q. All right. Dr. Cheresh, one second. I'm trying to get the animation up to where you are.

A. So this just shows the difference in tumor weight and that we actually had achieved a regression of these tumors by cutting off the blood supply. And this is the first time this had been ever seen and gave everybody, I think, in the field a boost that maybe angiogenesis therapy might be useful for cancer.

Q. So you were starting to talk about testing a second compound in this model?

A. Right. So we used a cyclic peptide to make sure that we weren't just seeing something that was just associated with the antibody per se but that really had to do with targeting [2030] alpha-v-beta-3. That was our contention, was that by interfering with the alpha-v-beta-3 with any kind of substance, antibody, peptide or organic, that you would have the same effect. So we had to scientifically prove to us that more than one class of molecule could do the same job. And that's, I think, what this illustration shows. And this, like I said, together with the antibody result in the regression studies was published also in that Cell paper in 1994, I think, December.

Q. And what happened after you added EMD 66203?

A. Well, the tumor shrank, the blood vessels disappeared, the tumor shrank, and, once again, regressed to a size smaller than we originally implanted in the first place.

Q. Now, you mentioned that you published these results. What is Exhibit 24?

A. Exhibit 24 is — that is the Cell paper, the 1994 Cell paper.

Q. And what was the title of that paper?

A. "Integrin alpha-v-beta-3 Antagonists Promote Tumor Regression by Inducing Apoptosis of Angiogenic Blood Vessels."

Q. And did you apply for a patent in connection with the tumor regression and use of LM609 and EMD 66203?

A. That's correct.

Q. And is that Exhibit 76 in your binder?

A. Yes, that's correct.

Q. Dr. Cheresh, I apologize, I believe I've misspoken here.

* * *

[2034] Q. All right. Now I'd like to switch subjects a bit and talk about the preclinical program from 1995 through 1998 with respect to the cyclic peptides. Okay?

But, first, let me ask you, did Scripps license LM609 to a company for development as a drug candidate?

A. Yes, they did. They licensed the antibody for development to IXSYS, a small biotechnology company in San Diego.

Q. And when did that happen?

A. I think that was in 1994.

Q. And did IXSYS then develop a drug candidate using LM609?

A. Yes, they did. They went through a process that they had been working with at IXSYS to humanize the antibody, to make the antibody go from a mouse antibody to a human, and essentially comparable to one of your own antibodies in

your own circulation. And the idea was to see whether or not, if we could convert it from mouse to human, would it still work and would it be effectively capable of interfering with human angiogenesis. And that was really, by that time, a goal of ours.

Q. Now, Dr. Cheresh, did IXSYS conduct preclinical [2035] experiments for some period of time after it licensed the antibody?

A. Yes, they did.

Q. How do you know that?

A. Well, I was involved in consulting with them on those matters and spent a lot of time looking at the data helping them work on experiments for that purpose, and I was very close, obviously, being in San Diego, had a very close interaction with them during that period of time.

Q. Now, how long did it take IXSYS to conduct the preclinical experiments regarding the antibody?

MR. FLORES: Objection, Your Honor, relevance and lack of foundation. This is an entirely different drug candidate than the ones at issue here.

THE COURT: What will be the relevance?

MS. THAYER: Well, Your Honor, this is not an entirely different drug candidate. This is a drug candidate that works exactly the same way as EMD 121974 as all of these witnesses have established. And the fact that the preclinical and now clinical development with respect to LM609 has

proceeded in a certain way, it's highly probative of the development of EMD 121974.

THE COURT: Mr. Flores?

MR. FLORES: Your Honor, these are entirely different compounds — antibody and a peptide. They are undergoing [2036] entirely separate and unrelated review processes in the FDA. Separate filing, separate everything. There are separate parties involved. I mean, it really couldn't be more different.

MS. THAYER: Your Honor, I don't think Mr. Flores has a basis, a factual basis, for what he has just said, that these are entirely different drug candidates going through entirely different review. There is no witness who is going to testify to that. Just to the contrary, the witnesses we will bring in, including ones that have drafted the IXSYS IND, including this witness, will tell you that they are extraordinarily similar and that the FDA —

THE COURT: Go ahead, if you can establish that predicate with this witness.

MS. THAYER: All right.

Q. BY MS. THAYER: Dr. Cheresh, let me ask you this: During the preclinical period for the IXSYS antibody drug candidate, did you have any interaction with the FDA?

A. Yes, I did.

Q. And, as a consequence of your interactions with the FDA representatives, did you learn anything concerning the pre-IND and IND process with respect to an angiogenesis inhibitor?

A. Yes, I did.

MR. FLORES: Your Honor, may I have a continuing objection to this line?

[2037] THE COURT: Yes, you may have a continuing objection.

MR. FLORES: Thank you, sir.

THE WITNESS: Yes, I did. I worked very closely with the head of the regulatory affairs at IXSYS, Kathy Estes, and we worked also together with the scientists to develop the experimental plan to present ultimately to the FDA, which was used to file an IND and ultimately lead to clinical trials, which, I believe, began in 1997.

Q. BY MS. THAYER: Now, Dr. Cheresh, I want to focus you on your interaction with FDA representatives during the '94 to '97 time frame. During those interactions did you simply discuss antibody — antibodies — as inhibitors of angiogenesis or did you talk more broadly about classes of compounds that are effective as inhibitors of angiogenesis?

A. Yes. We talked more broadly because both antibodies and peptides are both considered biologicals. And that's examined by the FDA more or less in a separate category as other agents. So we talked about the kinds of experiments

that were necessary to convince the FDA that we should go forward in the clinic.

Q. Now, any of your conversations with FDA representatives, did they distinguish between the type of data they would want to see in connection with an antibody inhibitor and contrast that with what they would want to see with an inhibitor of alpha-v-beta-3 that was a different type of a compound?

[2038] A. No, they did not.

MS. THAYER: Your Honor, I believe with this I have laid the foundation to go forward and ask a bit more about the preclinical program with respect to the antibody.

THE COURT: Well, it is my understanding that he may have conducted some research on the drug, but I'm going to require that a broader predicate be established concerning the extent of research on either one of these and whether or not they would distinguish one from the other insofar as the IND process is concerned, if he's able to establish that. Do you follow that?

MS. THAYER: I'm not quite sure. Could you state it again?

THE COURT: It's my understanding he testified that he conducted research on the peptide and the antibody and, as a result of this, there were documents that were published. What I've said is that you better go forward and establish whether or not progress could be made in one and not the other, the difference in time factors and the like. If they are

not compatible in terms of developing, then I will sustain Mr. Flores' objection.

MS. THAYER: All right.

Q. BY MS. THAYER: Dr. Cheresh, were you a consultant to IXSYS throughout the preclinical development period for the antibody drug candidate?

[2039] A. Yes, I was.

Q. And as a part of your job as a consultant, did you interact with the regulatory authorities?

A. Yes, I did.

Q. Did you help prepare pre-IND packages?

A. Yes, I did.

Q. Did you have discussions with FDA regulators during that period about the pre-IND clinical — preclinical work?

A. Yes, I did.

Q. Did you also play a similar role with respect to EMD 66203 and 84189?

A. Yes, absolutely. I had, since we had successfully moved the IXSYS program through the preclinical stages, I knew precisely the kinds of experiments and things that the FDA required of an angiogenesis inhibitor in terms of efficacy, specificity, pharmacodynamics, safety, toxicology. And many of those things were designed to simply duplicate for the Merck program, the idea being that we knew the path and there was no sense in rediscovering the wheel, because

we had already laid the path for the Vitaxin alpha-v-beta-3 inhibitor. So it was very clear what we had to do, and the fact that there was little difference in the approach we would take for the 121974.

Q. Now, in terms of the time frames taken to conduct preclinical experiments for the antibody and for the cyclic peptide, were the time frames required for the preclinical [2040] experiments different or the same given your interaction and involvement?

A. Well, I'm not quite sure I follow the question. The time frames in terms of what, the —

Q. How long it took to conduct the preclinical phases.

A. Yeah, I mean, I think that they are comparable. I mean, I can tell you Vitaxin, the humanized antibody, was licensed in '94 and was in the clinic in February of '97. And so that's a relatively short period of time. And the 121974, I don't know the exact dates, but they are, relatively speaking, comparable in terms of the time and the energy put in.

Q. And in terms of the types of experiments that were conducted in the preclinical phase, were those similar or different?

A. They were precisely the same. The only difference was, in one case we had the peptide and in the other case we had the antibody. For all intent and purposes, they were the experiments we published on and that had been discussed here, to some degree at least, some of those experiments.

* * *

[2042] Q. BY MS. THAYER: Dr. Cheresh, could you, once again, I think you've touched on this a little bit, but explain to the jury what experiments were conducted at IXSYS during the preclinical phase?

A. The types of experiments included in the in vitro experiments were receptor assays showing specificity, that the peptide had the specificity we said it did. Cell attachment assays, which had similar information provided, that is, we could show specificity for the alpha-v-beta-3. And then we moved in the direction of in vivo experiments, such as the chick CAM using the FGF filter disks that I showed you, the very same experiment, the tumor regression studies that I showed you in the chick CAM. And, in addition, we moved into the mouse experiments that I think we'll be talking about here in a minute where we placed human skin onto an immune-compromised mouse and measured human angiogenesis. And then finally, under GLP conditions, there was a — IXSYS was able to get an outside company to test toxicology, the toxic — toxicity, potential toxicity, of this in both rabbits and in [2043] monkeys.

Q. Dr. Cheresh, we'll get back to toxicology studies in a second. Let me just ask you, during the preclinical experiments at IXSYS, were any rabbit eye assays conducted?

A. Yes, there were some rabbit eye assays, I failed to mention also, that's correct.

Q. How about any rabbit tumor assays?

A. There were also tumors in the rabbit. There is a tumor that was developed by Dr. Folkman, once again, in this case in the rabbit. And we showed some efficacy studies there as well.

Q. Now, you've just mentioned the toxicity assays were contracted out to some other laboratory; is that right?

A. That's correct. They went to a GLP lab for that purpose, because, of course, we're not a GLP lab and they were not a GLP lab.

Q. When you say "they" were —

A. IXSYS was, I don't believe, had GLP capabilities nor did we. So they went and contracted the toxicology studies, which they went ahead and did through an outside laboratory.

Q. Now, do you know of your own personal knowledge whether the experimental data obtained from these assays you've just described, do you know whether they were submitted in connection with the IXSYS IND?

A. Yes, they were.

* * *

[2044] Q. Now, let's move now back to discussions about the cyclic peptide. After the research that you've talked about and shown here in connection with your animations, did you write to Merck regarding future work on angiogenesis inhibition?

A. Yes, I did.

Q. Would you look at Exhibit SK in your binder? And please tell us what that is.

A. That's a letter dated December 22d, 1994 to Dr. Alfred Jonczyk from myself. And that describes the goals of

our experiments and the types of studies that we hope to do and scale up.

Q. All right. I'm sorry, I just hit the wrong button here.

Let me ask you, were you here during opening statement when Mr. Flores made some comments about this letter?

A. Yes, I seem to recall some comments about this letter.

Q. Do you recall that he said what the evidence will show Dr. Cheresh was acting — asking Merck — at this point is, do you have something that can bind to alpha-v-beta-3 receptor and disrupt these attachments that's not a peptide? Do you have something that will do the job that's not a peptide at all? Which, of course, would be outside the scopes of the patents-in-suit here. Did you hear him say that?

A. Yes, I did. It was, I think, in referring to the last paragraph in this letter here.

Q. Is it true that you wrote this letter to Merck in order to [2045] tell Merck how it could get around the patents-in-suit?

A. Absolutely not.

Q. At the time you wrote this letter, had you ever seen any of the plaintiffs' patents?

A. No, I had not.

Q. Had you ever read any of the plaintiffs' patents?

A. I had not.

Q. Had you ever discussed any Burnham Institute patent with anyone?

A. No, I had not.

Q. Had you ever discussed more specifically any of the plaintiffs' patents with Merck when you wrote this letter?

A. No, I did not.

Q. In fact, did you discuss the patents in this lawsuit with anybody at Merck at any time before this lawsuit was filed?

A. No, I did not.

Q. Now, after you wrote this letter, did you send a proposal to Merck for a preclinical program at Scripps?

A. Yes, I did.

Q. And is that an exhibit in your binder?

A. I believe it's the next exhibit here.

Q. Could you read the exhibit lettering in the record, please?

A. Yes. That's Exhibit TD. That is the Scripps/E. Merck Program on Angiogenesis, with myself as principal investigator.

[2046] Q. And what did you do with this proposal?

A. Well, we submitted this proposal for review by the people at Merck.

Q. And what was the response?

A. The response was, rather shortly thereafter, was a very favorable response. They effectively funded the entire program we outlined in this proposal.

Q. Is the response in your notebook there?

A. I think it is. Somewhere it is.

Q. Why don't you look at the tab TI.

A. Yes, I see it here. Yes, I see it right here.

Q. And what is Exhibit TI?

A. TI is a letter from Dr. Sombroek to myself and was dated the 20th of February 1995, and indicating it is a pleasure, quote, it is a pleasure for me to inform you that within the pharmaceutical division of E. Merck we have come to an agreement to sponsor the program on angiogenesis as described in your proposal, Scripps/E. Merck Program on Angiogenesis.

Q. And what was your understanding of what's being referred to in these quotation marks here?

A. That is the title that I gave to that program. That is the title of our proposal.

Q. Before we move on, let me just ask you one more question about Exhibit TD, which is the February 1 proposal.

A. Uh-huh.

[2047] Q. Could you turn to the page 31398?

A. Yes.

Q. You included there a time scale. Do you see that?

A. Yes, I did.

Q. Why did you put in this proposal that a drug candidate, excuse me, that in the third year of clinical trials will begin?

A. Well, at the time we knew now we had a target. We knew that we could impact disease processes, a very important disease such as cancer, and the people at Merck and myself came to an agreement that this would be a reasonable time frame, an aggressive time frame, to do the experiments necessary to get a candidate into the clinic. And so we more or less developed a three-year time frame at this point, and that's what I outlined here in that paragraph.

Q. All right. Over the next three years that this program was funded by Merck, what was your role in the preclinical program?

A. Well, to a number of things. Certainly work on these assays establish the parameters of angiogenesis inhibition, determine the dosing, the efficacy, evaluate some of the pharmacodynamics, helping the Merck people do some experiments as well, evaluating some of the studies, both myself and Merck were doing, and really meeting with Merck people and trying to push this project toward the clinic as rapidly as we could.

[2048] Q. Dr. Cheresh, I'd like to now focus on 11 categories or types of experiments that have been accused of infringement in this lawsuit, and ask you just a few questions about those 11 categories.

In your binder is there a chart that lists the categories?

A. Yes, there is, I believe.

Q. I'm wondering if I might borrow that from you so I could put it up on the Elmo and everybody else can read along with us. Tell you what, let's just focus that on the — we've got here the experiment category and summary. And I'll ask you —

MS. THAYER: Excuse me just one second, Your Honor. I'm trying to see if we have an extra copy of this.

Q. BY MS. THAYER: I'm just going to go through the categories of experiments in connection with the cancer applications leaving aside the arthritis and the eye models for which we have already heard some testimony. Could you please, and I'll take it category by category, tell me why this particular assay was conducted during this period of time? In other words, what sort of data were you hoping to get out of these assays?

A. Could you focus that just a bit? Is there a possibility of getting that a little sharper?

Q. I certainly can't, but Ms. Weil may be able to. I've also got a copy that I can give to you and maybe that will make it a [2049] little easier.

A. Thanks.

Q. Let's start with alpha-v-beta-3 binding assay. Why did you include that in the preclinical program?

A. Well, this simply speaks to the idea of efficacy. It allows you to pick the best peptide and really describe with precision how active the peptide might be with regard to this target.

Q. Over this period of time did you compare any of the three cyclic compounds that Merck had developed to compare their effectiveness in this assay?

A. Yes. Well, for example, you could compare different compounds and determine which one was the best. And also, by using different integrins coated on the plate, to determine which ones were more specific for a different integrin. And it becomes very important if you're going to develop a drug to make sure that you have a candidate that doesn't inhibit the wrong receptor.

For example, if it inhibits the 2-B-beta-3 receptor and you inject that into a patient, they will bleed, and they could bleed to death. And so it becomes very important that you pick a peptide or antibody or a compound, whatever it is, that is specific for the receptor you're looking at. Like I said, if the 2-B-3 receptor, that's a no no, and we want to eliminate that. So if we used a combination of multiple receptors in [2050] this assay to select the ones that were targeting the alpha-v-beta-3.

Q. Now, let's go down to the angiogenesis chick CAM assay. Why did you include this assay in the preclinical program?

A. Well, that tells you something about both efficacy, safety, mechanism of action, and, to some degree, do some screening there, some light screening. And the reason it tells you, of course, about efficacy is that, as I showed in the demonstratives earlier, that you do get tumor shrinkage and blockade of angiogenesis. Safety, we showed that the chick embryos were just fine,, the tumors regressed but the chick embryos went on to develop normally. So that pretty well tells you the drug was safe.

Q. Dr. Cheresh, let me stop you because this may have been a little bit confusing there. There are two different entries on this chart because there is, then, two different categories set up in the notebooks prepared by plaintiffs. So we have one that is tumor growth chick CAM assay that we'll get to in a minute.

A. I see.

Q. This one is simply the angiogenesis inhibition without the tumor. So given that, should I change any of the checks here or would your testimony be the same?

A. Oh, it would be the same because, once again, you're still evaluating the pre-existing blood vessels. If it was targeting [2051] all the blood vessels, then it would kill the embryo and be toxic to the other blood vessels. Efficacy allows you to determine, that, in fact, you're targeting only the new vessels, once again. Mechanism of action, we use this model to show that the peptides or antibodies were causing programmed cell death or apoptosis of the angiogenic endothelial cells. And with regard to candidate screening, certainly we could determine more than one compound, more

than one peptide or antibody could be tested on a batch of chick embryos. So, yes, these four — I imagine you could also get some information regarding the pharmacokinetics, because there you could determine the dose required to get inhibition of angiogenesis. So we —

Q. Do you recall whether or not you did vary the doses used in connection with this assay?

A. Absolutely. So we ran in different groups of range increasing dose of the peptide to find out what the minimal dose would be to see the effect. And that was a standard procedure. Because this dosage gave us some clue as to what ultimately we might expect to see in the circulation of a patient perhaps getting the drug.

Q. All right. Let me then move down to the next type of experiment, angiomatrigel. Why did you include this in the preclinical program?

A. Well, this is important because now we moved from the [2052] chick to the mouse, and the mouse is a mammalian species, so it is closer — mice are closer to us than chicks. So in this case we used an injection of a matrix protein, sort of a gel, that had the growth factor within it, same growth factor that we used in the chick CAM, to put now into the mouse. And just like they did on the chick CAM, the mouse blood vessels would invade this area. And we could now examine, by giving a systemic injection of an antibody or peptide or compound that was directed to alpha-v-beta-3, and examine the effect on angiogenesis now in a mammalian specie, not just a chick embryo anymore. So now we're really in a living mouse that would tell us something more about what happens in a mammal.

Q. And did the data that —

JUROR: Is there any way you can focus that? That's really bugging me. I would really like to read what's there.

THE WITNESS: I think it's maybe on the — there we go.

Q. BY MS. THAYER: All right. Dr. Cheresh, in terms of the categories that you've been talking about with the other types of experiments, what did the data from these assays that you just described, what did that tell you either about safety or efficacy or any of the others?

A. Well, that we had an efficacious compound that was safe to inject and that had a particular mechanism of action that we could point to and describe and define in reasonable terms. We [2053] could also use these assays to test more than one compound to really identify what might be the best of these variants. So if we had several different versions of a peptide or antibody or an organic compound, we could use these assays reasonably quickly to find out, well, which is the best angiogenesis inhibitor and which is the safest, which causes the least problem. Like I say, if we had used a IIb IIIa inhibitor, we would expect to see bleeding. And so, in that situation, we would steer clear from such a compound.

Q. Dr. Cheresh, you say you could use this type of an assay to compare candidates. Did you, in fact, use this assay on more than one of the Merck compounds?

A. Absolutely, that's correct.

Q. All right. Let's now move down to cell adhesion assay. Why did you include that in the preclinical program?

A. Well, this was a biological assay that was somewhat more biological than the receptor assay but still in vitro and allowed us to more rapidly screen multiple compounds in getting us a sense for what would happen to the adhesive state of the cell when we allow these cells to incubate with the peptide or antibody beforehand, and what was the effect on the cell in terms of attachment, subsequent attachment. And this was important because it verified the receptor binding studies.

Q. You just used the word "screen." Did you use this assay to screen candidates in the sense that you talked about [2054] screening at pharmaceutical companies last week?

A. Well, what I was referring to, of course, is using multiple compounds in a relatively short-term, easy-to-define assay, yes.

Q. But how many compounds did you, in fact, test?

A. Limited number, 15 or less.

Q. I'm going along and checking boxes here as you testify. Could you tell me — I did hear you talk about candidate screening with respect to the cell adhesion assay. Did you mention any of these other categories?

A. Let's see. The efficacy — one could think of safety, because if you put something in that blocks cell adhesion or was toxic to the cell directly, then you'd want to see that too. I mean, there are various things that could happen. You could

put a poison on the cell and it may have an effect on the cells indirectly. So, yes, you could say safety to some degree. Efficacy certainly. Mechanism of action would tell you about the cell itself and what was happening to the cell. And, ultimately, some degree of candidate screening could be done here.

Q. All right. Then let's go to the next category, chemotaxis. Why did you include that in the preclinical program?

A. Well, in this case this actually had more to do with the arthritis studies that Dr. Storgard was doing in my [2055] laboratory. And we used peptides to interfere with angiogenesis during arthritis and we wanted to know whether or not any of the effects that we saw were associated with the prevention of lymphocytes or leukocytes migrating. I need to back up a bit and explain that, when arthritis develops, that's an inflammatory disease. An inflammatory disease is characterized by an infiltration of inflammatory cells like leukocytes that create a lot of the trouble that we think about when we think about arthritis.

And so we were saying that the peptides that Merck provided were inhibiting angiogenesis, and, therefore, inhibiting arthritis. We had to rule out the possibility that those peptides were simply interfering with leukocyte migration, which could have also explained why we were receiving such a nice anti-arthritic effect.

So what we did was we developed experiments to measure in vitro the migration of leukocytes in response to chemical substances in the presence of the same peptide. And

what we discovered was these peptides did not interfere with leukocyte migration. So we then concluded that the reason why the peptides had the anti-arthritic effect was because they blocked angiogenesis, not because they interfered with *leukocyte migration.*

Q. Did that information shed any light on mechanism of action?

[2056] A. *Absolutely. It told us that we were, in fact,* targeting the blood vessels in response to the arthritic disease.

Q. And, finally, did this particular type of assay shed light on safety or efficacy?

A. Well, it told us that we weren't going to impact the immune system to any great degree. If there was an infection someplace, we wouldn't expect necessarily to see an inhibition of infection response by leukocytes, for example. You don't want to wipe out your immune cells and that would cause immune deficiency. We don't want to do that. We just want to hit the angiogenic blood vessel. So this was an in vitro test to determine whether or not these immune cells might lose their migratory capacity. And we didn't want to get — we didn't want to have that happen.

Q. All right. Let's turn to the next category, chick embryo pharmacokinetics. Why did you include this assay in your studies?

A. Well, because, as you recall, I mentioned that we were doing dose response sort of studies, where we increased the dose, went with one group of embryos, and increased it with another group. And we wanted to evaluate and make sure we

knew how much peptide was in the circulation where we saw the anti-angiogenic effects. It's one thing to inject a drug. It's another thing to find out how much drug is there in circulation and how long it's there. So we needed to have that [2057] information to know what we would expect to ultimately have to see in a patient, how much actually in the bloodstream do we need to see.

And so what was done was to bleed the, take some blood out of the chick embryo at various times after we injected the peptide, and then have that blood evaluated for the presence of the peptide. And this told us at any given point in time how much peptide was there in the circulation while the angiogenesis inhibition was ongoing.

Q. Now, what did that tell you either — about any of these categories that we've been talking about in terms of either candidate screening or pharmacology or efficacy or — what did that relate to?

A. Well, it related to the pharmacokinetics. It told us about the level required in the circulation to see the effect we have attempted to see.

Q. By the way, Dr. Cheresh, I note that this single experiment was done in 1994. Do you see that?

A. Yes, I do.

Q. Of the experiments accused of infringement in this case, are there any other experiments in the 1994 time frame that you believe were part of the preclinical program as contrasted with your basic research?

A. Not that I'm aware.

Q. All right. Now, let's talk about FACS. Why did you [2058] include this in the preclinical program?

A. Well, this was a — this is a mechanism to determine the activity of a peptide when bound to a cell. And so we actually used a penton-based co-protein — I don't want to go into great detail here, other than to say we used a naturally occurring RGD-containing protein from a virus and we used this to evaluate the activity of the receptor. All we did in this case was to determine whether we could measure the occupancy of that receptor when it was exposed to the peptide. And in this case, I think, we also did some inhibition of ligand adhesion, essentially a way to measure cell surface associated peptide.

Q. Did this shed any light on mechanism of action or efficacy?

A. It told us about the efficacy and it told us something about the mechanism of action, that's correct.

Q. Now, let's move down to rabbit pharmacokinetics. That would be on the next page. Again, I have skipped over the experiments — mice arthritis, mice retina, mice retina/vasculo — because we have already heard testimony about that from Dr. Friedlander. But, wait, let me ask you this one question about mice arthritis, because I don't think that was covered with Dr. Storgard. There is one experiment there, mice arthritis.

Why did you undertake that experiment during this preclinical program?

[2059] A. Well, we were attempting to get a second animal model for efficacy testing in the arthritis experiments.

We knew that we could block the arthritis process in the rabbit knee, and we attempted to do this with a second model to make sure that we had a solid basis for going forward in the arthritis area. I might also point out that the mice are much — much easier to work with than rabbits and much more inexpensive. So it would have been very helpful for us to do some additional work in the mouse model and would give us a lot more information about mechanism, safety, efficacy, and other things that we could do in parallel, because the mouse studies we could do very rapidly. The rabbit studies took quite a long period of time.

Q. All right. Now, let's then go to the third page of this chart and let me ask you again to look at — let's see, rabbit pharmacokinetics. Is that Dr. Friedlander or your laboratory?

A. That would have been Dr. Friedlander.

Q. All right. Let's go down to tumor growth, chick CAM assay, then. Why did you include that in the preclinical program?

A. Well, this is, of course, as I said earlier, is really something that we did routinely to prove that the effects that we were observing on the blood vessels had an impact on tumor growth, that at the end of the day we were interested in treating cancer parents. And so we wanted to know did the test compounds have a particularly good anti-angiogenic/ anti-tumor [2060] activity and were these things related. So we used the M-21 L-cells, and these are the cells lacking alpha-v-beta-3, once again, to no mechanism of action. Did we get tumor regression? If so, if it happened in this model, we knew it had to be due to the anti-angiogenic effect, not

an anti-tumor effect. Very important distinction, because it told us the target and it gave us some insight into mechanism, of course, safety, efficacy. And we could do some degree of screening here. We could compare three or four compounds at a time in this model as well.

Q. All right. Let's move down to tumor growth in SCID mouse. Why did you include that?

A. Well, we included that because that is probably as close to human angiogenesis that you can get without actually going to one of your postdocs and asking to inject the peptide or compound in their arm.

Q. In the past, in talking about this assay, have you created a demonstrative that shows how this assay works?

A. Yes, I have.

Q. All right. I'm going to put that on the Elmo here.

A. Maybe you could make it smaller, I think.

Q. I will try and do that.

A. And refocus, if we could. Well, I can read it. I mean, I know what it says, I think.

Q. So, just briefly, what is it — how is this assay [2061] constructed?

A. We start with a mouse that is immune compromised so it doesn't have any immune system to reject foreign tissue. And we transplant onto that, onto the back of that mouse, human neonatal foreskin. So when little boys go in when

they are born and their foreskins are removed, we get those. Rather than having them thrown away, we get those from the surgeon directly. And we can transplant that tissue onto this mouse. And because this mouse's immune system has been wiped out, we can measure — this will actually grow. It will grow as part of the animal, as though the animal was growing human skin.

Q. When you mentioned that the immune system is knocked out, that you use a mouse like that so it won't reject human skin?

A. That's right. If you used a normal mouse or a normal animal, it would reject the foreign graft. And so this mouse doesn't do that. And we grow — of course, we keep these mice in very special sterile containers, in sterile cages, so that they don't get infections. So what happens during about the three or four weeks after we transplant, a very interesting process occurs, and that is the blood vessels that are in the skin that we transfer from the human skin to the mouse connect with the mouse vessels. And now you have a direct connection between the mouse vasculature and the human vasculature within the skin. So now what you have is you have, in the skin of the mouse, a human, full vascularized tissue that's got human blood [2062] vessels. And we proved they were human blood vessels with antibodies that are specific for the human receptor.

Q. Now, in this assay what do you do after you put the human skin on the mouse?

A. Okay. So then we inject into that skin a human cancer directly into the skin and allow it to grow. And then what we

show is that that growth depends on human blood vessels in the human tissue in response to the human cancer. So now, for all intents and purposes to any pathologist that would look at this tissue, they would say that's a human cancer in a human tissue.

Q. And then what do you do?

A. And then we treat, in this case, with the LM609 or cyclic peptides directed to alpha-v-beta-3. And what we observed and published a number of years ago was that this, in fact, did cause shrinkage of tumors, it caused interference with the angiogenesis of those tumors, and that it changed the biological property of the tumors rendering them incapable of invading and proliferating. So this, of course, speaks to efficacy, mechanism of action, safety. And also routes of administration, we were able to inject the mice different ways — subcutaneously, directly into the bloodstream, intraperitoneally, and determine the route of best administration of the drug. So we actually did this in different ways and found the best way to inject.

Q. All right. Let's move to the last type of experiment, [2063] tumor growth chick — I'm sorry — tumor growth nude mouse assay. Why did you include that in the preclinical program?

A. Okay. Now this is a mouse that is immune compromised as well, where now we put a human tumor in directly. In this case we're directly allowing the mouse vessels to get in without manipulating with a piece of skin. So, in other words, this is just like you have a human tumor growing in yourself in some ways, in that your own blood vessels

invade. So in this case now we're measuring the ability of the mouse vessels to invade the growing human tumor. And we're using, then, injections of the peptide directed to alpha-v-beta-3 to block that process. So in one case we were hitting human vessels; in the other case we're now hitting mouse vessels. And in both cases we observed the same degree of efficacy, that is, if you had an alpha-v-beta-3 inhibitory peptide or antibody, you would see that type of activity. And it also spoke to pharmacology, pharmacokinetics, and mechanism of action.

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APPENDIX 45 — TRIAL TESTIMONY: CROSS EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY DEFENDANTS ON MARCH 2, 2000

[Commencing at page 2156]

Q. And, in fact, your claim is limited to the use of RGD peptides, isn't it?

MS. THAYER: Same objections, Your Honor.

THE COURT: He can answer that question.

THE WITNESS: As far as there are obviously some, you know, in Claim 1 — are you referring to Claim 1 specifically?

Q. BY MR. FLORES: I'm referring to Claim 1, that's right.

A. In Claim 1 it appears that it requires an RGD-containing alpha-v-beta-3 antagonist.

Q. And the reason that the RGD sequence is important is because that's important to the binding between the peptide and alpha-v-beta-3, correct?

A. Well, it seems to be important, once again, in terms of the activity of the peptide to prevent adhesion through the alpha-v-beta-3 receptor. So, insofar as that sequence has been shown to be important, this is an example of an important peptide sequence that has that activity.

Q. In going back to your discussion about linear peptides, didn't you in your patent here state that one of the preferred embodiments of your invention using RGD peptides to inhibit angiogenesis would be the use of a linear peptide?

A. You know, I don't recall the specifics. Once again, I didn't draw up the patent claims. This was done by a lawyer. But that may well have been in there. I'm not sure.

Q. Well, let's see. Take a look at column 17.

[2157] A. 17?

Q. I'll show you where here. This paragraph beginning around line 38 or so. "A particularly preferred peptide synthesis method" —

A. I think it's preferred cyclic peptide, is that —

Q. Cyclic peptide, that's right. And it says, particularly preferred peptides for use in the present methods, and then it lists some peptides? Do you see that?

A. Yes.

Q. And among the peptides listed as particularly preferred peptides for use in the present method is a linear peptide right here, right?

A. That long one, yeah. I suspect that's correct.

Q. Now, you did review this application for accuracy, didn't you?

A. Well, I read it over, that's correct.

Q. And, in fact, wasn't this application drafted by counsel based on a manuscript that you submitted to the Scripps patent lawyers?

A. In part, that's correct. But I don't believe we have ever tested that particular peptide. I'm not sure that I've tested it specifically.

Q. Now, you have had the opportunity to test a variety of different peptides with different sequences that will antagonize alpha-v-beta-3 and thereby inhibit angiogenesis, [2158] correct?

A. That's correct.

Q. And you've tested a lot of different peptides with a lot of different sequences, haven't you.

A. We have tested — well, I have not tested a lot of different peptides myself or in my laboratory. We had — the Merck people had done some extensive screening along those lines. But we work with a rather limited number of peptides.

Q. Well, that extensive — the results of that extensive screening work is the RGD peptides that worked, right?

A. In most cases, that's correct.

Q. And that's why it's limited to RGD in this patent.

A. Well, like I said, in this case we were showing only the examples that we had examined and tested. And so from what my understanding is of being able to write a patent is you can't claim something that you haven't shown. And so the idea here is that what we had worked with was RGD

peptides, so that's what we would put in our patent. This is a use of that particular structure.

Q. So the reason that the patent claim requires RGD peptides is, that's the only thing you've been able to show works.

A. No, I wouldn't say that. I said that's all we showed at the time. That was that one class of compounds that we were working with at the time that we had an example of that was definitively able to block alpha-v-beta-3 and inhibit [2159] angiogenesis.

Q. Okay. Let's go back to the FDA. I think you've agreed that you're not an expert in FDA regulations for purposes of drug approval, correct?

A. Well, the only thing I can, like I said, claim some expertise in is what was required on behalf of the experiments that we were involved in. My direct interactions with the FDA had to do with what they had asked us to help them with.

Q. Okay. Well, you certainly understand your own experiments, right?

A. With respect to the FDA, that's correct.

Q. But my question is, are you an expert in the FDA regulations and the process?

A. I am not an expert on FDA.

Q. Now, I think you testified a couple of days ago when I first examined you that your laboratory is not a GLP laboratory. It's not served as a GLP laboratory?

A. That's correct.

Q. GLP stands for good laboratory practice.

A. That's correct.

Q. And those are some very specific requirements that the FDA has for laboratories that submit data to the FDA.

A. Well, as I understand it, that when there is a requirement for GLP, that you must use a GLP lab. But not all data that is included in FDA submission is required, is requiring the GLP.

[2160] Q. Well, you — I'm sorry.

A. No. So I was simply saying that what I recall from my discussions was that the toxicology data provided had to come from a GLP lab. But the efficacy data did not have to come from GLP. And both of them were included and necessary to support the FDA clinical trials that we're talking about.

Q. Well, you've known all along that Merck would have to submit data from a GLP lab in order to get approval. Some GLP data would have to be submitted?

A. At some point there would be some GLP data submitted, but certainly not exclusively.

Q. Now, back in 1997 you were not aware of what the concerns the FDA would have about non-GLP work, were you?

A. I'm not sure. I'm a little confused on the question.

Q. Well, your work, all your work is non-GLP, right?

A. That's correct.

Q. And you weren't aware of to what extent the FDA would be concerned with non-GLP data.

A. Well, no, I don't think that's correct. In fact, by 1997, based on my knowledge of what had happened at IXSYS, those clinical trials began in February of 1997, and the IND was filed in December of 1996, which I had a hand in preparing. So the data that I was aware of even before 1997 and the information that I was aware of in 1996, while those discussions and the pre-IND discussions were ongoing, was that [2161] there would be a substantial amount of the data included in that IND that involved chick CAM, cell adhesion assays, receptor binding assays, and mouse studies that were all done under non-GLP conditions, and that the GLP experiments were rabbit toxicology and some humunculous monkey toxicology studies.

Q. So your testimony now is you were aware in 1997 the extent that FDA would be interested in this non-GLP —

A. I was simply aware of what was being compiled for the IXSYS IND that was being included and ultimately prevailed in a — in allowing the clinical trials to proceed.

Q. I would like to read from Dr. Cheresh's deposition at page 390, lines 14 through 24.

Question. Let me — do you have an understanding about under what circumstances the FDA is interested in non-GLP data?

Answer. My impression is it varies based on the type of experiment and the type of drug being evaluated. And there is no particular rule that applies to — in a blanket way — that applies to preclinical data.

Question. Okay. Now, in the particular case of the cyclic peptides that are under development that you're involved in, what understanding do you have about the extent to which the FDA is interested in non-GLP data?

Answer. I have — I am not aware of their particular [2162] concerns about GLP pertaining to the work in our laboratory.

Question. Have you discussed that issue at all with anyone from the FDA?

Answer. No.

So is it correct, then, sir, that as of the date of this deposition, which is August 1997, you had not discussed with anyone with the FDA the concerns that the FDA might have about the use of non-GLP data for purposes of the cyclic peptides that Merck has under development?

MS. THAYER: Objection, assumes facts not in evidence.

THE COURT: That objection will be overruled.

THE WITNESS: What I was referring to, because the discussion was centered around the peptide, and I had not at the time had specific discussions with anybody pertaining to the FDA. And what I had already, of course, told you was what I knew about the antibody data. And so based on the specific example that was put forth to me at the time of my deposition, that's correct. But with respect to the general aspects of FDA filings, clearly, we had an example where the antibody was used and experiments were used to include non-GLP.

Q. BY MR. FLORES: It was your understanding at the time, sir, wasn't it, that the FDA level of concern or the nature of FDA's concern about GLP data would vary with the type of drug being evaluated, correct?

[2163] A. Well, I think that — yeah, that's fair to say. In the broad context of the FDA, that there would be some drugs that would require different input based on the idea. Because I think the mechanisms of actions would be very different, the toxicology issues would be different. Delivery strategy, it would be different, clearly, than a peptide or an organic molecule. All these have to be considered very separately and differently. And based on my discussions with respect to the antibody and the target alpha-v-beta-3, it was quite clear, given the antibody example, that non-GLP experiments including CAMs and receptor assays showing efficacy were very welcomed by the FDA. And with respect to the peptide, I had not at that time acquired any information.

Q. So you didn't know.

A. That's correct, with respect to the peptide.

Q. Right, with respect to the peptide, you didn't know.

A. That's correct.

Q. Now, we've talked about the differences — for my next question, I'm just going to — I'm referring to antibodies and peptides that are antagonists of alpha-v-beta-3 and you use them to inhibit angiogenesis. Okay?

So, within that framework, we have already talked about how the FDA processes antibodies as biologics and synthetic peptides as drugs. And that's separate, right?

A. That's right.

[2164] Q. Now, from a biological perspective, there are also significant differences between the antibody and the synthetic peptides, aren't there?

A. Well, it depends on what you mean by biological perspective. I would contend that they work in precisely the same manner in terms of their inhibiting angiogenesis and having the effects they do on tumor growth. So you could argue that they are different structural entities, but they target the same receptor on the same cell type causing the same programmed cell death causing the same anti-angiogenic process causing the same tumor regression. So insofar as there are two different forms of analgesics, for example, they would be both having similar activities in terms of getting rid of your headache. So, in many ways they work, in fact, on the same, virtually the same receptor.

Q. But there are differences, aren't there?

A. Absolutely. They are two different entities.

* * *

[2173] * * *

Q. It says here, we will examine the role of integrin antagonists on vascular cell signal transduction. And what is cell signal transduction, sir?

A. Well, with respect to the integrin antagonist, that is, the information that is passed across the membrane by way of the integrin. You've heard some of that earlier in the discussions. We know that those signals are responsible now for cell survival and cell proliferation, among other things. And so it was important for us, in order to establish the [2174] efficacy of these compounds, to have assays in place that allowed us to determine whether the integrin antagonist was, in fact, interfering with a signal transduction mechanism. So as part of our efficacy direction, our goal was to evaluate some of these read-outs, including vascular cell signal transduction.

Q. Dr. Cheresh, you say "these compounds." By "these compounds," you mean any compound that inhibits angiogencsis based on being an antagonist of a vascular cell integrin, correct?

A. Well, with respect to the ones that we ultimately focused on, I mean, the goal would be, you couldn't do a complete research project on each of a hundred compounds. What you would have to do is narrow it down and then

evaluate a limited number of compounds in a number of different parameters, including signal transduction and some of these other things I've listed.

Q. But you hadn't narrowed it down when you made this proposal, when you wrote this document.

A. Well, we had come down to a reasonably small number. I mean, I think, like I said, at the time we were so far down as to, although we couldn't anticipate exactly where we were going to go here, because this was a grant proposal, not a — this was not a report of research results. This was in anticipation that we might get something more potent, more specific. And [2175] that was our ultimate goal, because we felt that if we were able to get something more potent and more specific, it would lead to a safer and more efficacious drug. But I think, as it turned out, we were not very far from the mark, because we did develop the 121974, which is really essentially an analog of the 85189, meaning they were essentially the same structures with a slightly different salt composition.

Q. But as you wrote this document, sir, weren't you proposing here in aim 3 to do some general research on how the role of integrin antagonists on vascular cell transduction, et cetera, et cetera? That's basic research, isn't it, on how all these things work?

A. Insofar as, you know, with respect to the Merck goals. Once again, I'll try to clarify this. The candidates, when we wrote this particular proposal, we did not have in mind the idea that we had the end, final best product. And there may be better ones that come along from here on out. But when

we identify something better, the goal would be to put it through some of the tests that we typically do in the laboratory, so as to really know whether we have the best candidate or not. I didn't want to say in 1995 that this is the best candidate, we're going to close our mind to anything else. That's not the way either science or clinical development would be best benefited, I think.

Q. Well, the way you wrote this, what you were suggesting to [2176] Merck is, let's go out and do a lot of research and see if we can find something and find a lot of things and see which one's better.

A. No, I don't think that's the goal at all, because, as you — if you read up in the top of that aim, it focuses on the — the clear focus here is the role of alpha-v-beta-3 and/or alpha-v-beta-5. I think the key element here is, at 1995, we're beginning to appreciate that alpha-v-beta-5 was to play a role in angiogenesis. And this became — this was something that evolved from studies ongoing in the laboratory. And so we wanted to make sure that we included the alpha-v-beta-5 as part of the equation. We didn't want to develop an inhibitor that was purely going to target alpha-v-beta-3 and miss half of the angiogenic cascade.

For example, we learned during our research efforts that growth factors such as VEGF, which I think you can see is there in paragraph 3, the second of the growth factors, that particular growth factor activates an alpha-v-beta-5 dependent angiogenic cascade. We were just beginning to learn that. And so at the time, when we went to Merck to propose these studies, we wanted to make sure that we included the analysis of structures that had alpha-v-beta-5

activity as well as alpha-v-beta-3 activity. And so I didn't want to narrow ourselves down to an alpha-v-beta-3 selective compound and miss out on all the tumors that produce VEGF or, for that matter, [2177] TGF alpha. And that would have been short-sighted on our part. And, in fact, based on the fact that we didn't narrow our scope too quickly, we did ultimately develop a dual specific inhibitor of alpha-v-beta-3 and alpha-v-beta-5 that Merck is taking now forward.

Q. Okay. But at this point you did not want to narrow yourself down.

A. We wanted to focus to some degree but not to the final individual compound. I think that's — that's clearly the goal.

* * *

[2180] * * *

Q. Now, as you wrote this proposal, Dr. Cheresh, it is not an outline for preclinical development of any specific compound, is it.

A. Well, it is, like I said, a general outline of scientific experiments. The goal here is to, as we have outlined quite [2181] clearly, is to have a candidate in the clinic by the end of this particular period of time. And the purpose of this is to define our role in this process to the best of our ability. Of course, when this was written at the end of '94, early '95, this is what we perceived would be the, included arrangement in terms of the science, from our point of view.

With respect to what was actually done and how much actually one gets done in a grant is quite different from what you may propose. You always propose a broader topic than you might actually accomplish so that you can keep it very flexible. And the goal here is to keep it flexible to take advantage of the observations as they are made. And most grant applications, I would say, if one is lucky, they get done 50 percent of what they propose and they do another 50 percent of what they hadn't proposed. And this is just an idea, just a rough outline, to give us a general guideline on where we want to go.

Q. Now, after you drafted this document and forwarded it to Merck, I think you said that there were further discussions about it.

A. No, I think — I think, as I recall, that — I'm not sure whether there were further discussions, but this was pretty much accepted on February 20th, I think, by a letter from Dr. Sombroek. So, in essence, this general game plan was put into place on the 20th of February from Merck's point of view.

[2182] Q. Now, you met with representatives of Merck in New York in April of '95. Do you recall that, sir?

A. You know, I may have.

Q. Do you have Exhibit 36 there in your binder? If not, I'll give you a copy.

A. I'm not sure I have 36.

Q. You probably don't.

MS. THAYER: Counsel, may I have a copy?

MR. FLORES: Yes.

Q. BY MR. FLORES: I'll give you a second to read that over, Dr. Cheresh, or however long you need.

A. Yes. I think this was a letter — this is a letter by Dr. Sombroek. I'm trying to see the date on here. It would be April 13th, 1995.

Q. And this is a letter that Dr. Sombroek wrote to you.

A. Yeah. I think this was more or less to verify the level of funding for year one, two and three, including all the dollar amounts and some suggestion about some of what was going to be going on at Merck at the time and what was going to be going on at Scripps or what we were going to do at Scripps.

* * *

[2184] * * *

Q. And what Dr. Sombroek goes on to propose here is — he says you might consider the following — do you see that? And he says, "Merck will take care of toxicological studies once we have defined a product for the pipeline." Do you see that language, sir?

A. Yes, I do.

Q. And at that time, consistent with what you've testified about your proposal, you had not yet — Merck had not yet — defined a product for the pipeline, had it.

A. Well, no, actually we were very close. Maybe I can explain what it means to develop a product for the pipeline, to define that term. That — and Merck undergoes a very special series of meetings and goes through a very special series of committees. Merck limits themselves to, and you can probably hear this as well from Merck people, but limits their actual pipeline entries to a very few per year. And so when they ultimately choose a final product, that means they are going all out. That means this is the thing they are going to put a heck of a lot of resources behind. When it gets into the pipeline, it's going to face clinical trials, and they are making hundreds of millions of dollars of the commitment to this drug. That's my understanding. And that goes through a long, arduous process of committees and evaluations and committees and goes right to the top of the company.

[2185] So when something is finally decided to go in the pipeline, it's been evaluated in extreme detail. And what we had here, of course, at this point was some one or two candidates that we were hoping would get to that stage, and ultimately we were successful in getting one into the pipeline. So that's what it means by the pipeline. It should really be defined.

Q. So your testimony is at this point in time, in April of 1995, it had been limited to one or two candidates?

A. Well —

Q. Specific drug candidates?

A. Well, let me phrase it this way — we were focusing on the 85189 and ultimately the 121974, I believe, at this time already. And it wasn't clear that this would be the only one we would develop. It wasn't clear that there would only be one drug that would come out of this work. And it still was not clear in early '95 that this was absolutely the best that we had. And I'm not sure that the pipeline commitment wasn't — was still a year or two away.

Q. You mean the decision as to proceed with a specific product was still a year or two away.

A. Well, I think they knew they were going forward with it, but, once again, the pipeline commitment is a sort of a final commitment, from what I understand. And it doesn't mean that they won't be doing lots of preclinical work and getting the [2186] preclinical work in line, but that it's really the level of commitment, long term, to this.

Q. Well, after Dr. Sombroek wrote this sentence about, "Merck will take care of toxicological studies once we have defined a product for the pipeline," he went on to say that pharmacokinetics, pharmacodynamics and biodistribution studies will routinely be performed by our institute in Grafing — is that how you pronounce it?

A. That's right.

Q. That's one of the Merck facilities in Germany?

A. Yes.

Q. — unless we ask you to help because of capacity problems. Do you see that, sir?

A. Yes, I do.

Q. So it's your understanding at the time that, once a product was defined for the pipeline, as far as however Merck understood that term, they would take care of those studies — pharmacokinetics, pharmacodynamics, and toxicological studies?

A. Well, this was, I understand it, a way to divide up the effort. We, as a small laboratory, could not do everything involved in pushing this forward. So the goal was to try to find where their strengths were and our strengths were and to put our heads together and divide up the labor appropriately. And certainly they were in a position to do certain things like the pharmacokinetics, pharmacodynamics better than we were.

[2196] * * *

Q. But other than the plans that we have already looked at, [2197] do you have anything that's written that's any more specific, that's focused in on any specific drug?

A. Well, yes, we do. We have the Theradex Reports that have — that show clearly all of the data compiled in a manner that allows us to speak to these various categories.

Q. The Theradex Report is not something you authored, though.

A. Well, we had a lot to do with writing them up. Like I said, we went over several drafts and we also provided the

data. So, in as far as all the data from the Theradex Reports, came directly from my laboratory.

Q. Theradex Report is a summary, isn't it?

A. Well, it's a — not entirely. It's a compilation of individual experiments that are compiled for easy-to-read access by regulatory agencies. So it's a way to put the data in tabular form. Sometimes the data in the lab notebooks can be a bit rough and hard to follow. It's a typed up version of what was directly in our laboratory reports.

Q. It doesn't lay out a future plan of action, does it?

A. Well, the Theradex Reports are not designed to do that. It's designed to report what we have done.

* * *

[2201] * * *

Q. Well, I'm asking about the toxicology studies for that specific compound. They have been performed, haven't they?

A. I believe they have.

Q. And they have been performed by Merck?

A. Well, part of the, believe it or not, the toxicology was — in Europe there were clinical trials that started sometime ago, as I understand it, perhaps maybe a little bit earlier, and that some of the toxicology was based on the human experiments as well as some rabbits and monkeys, I believe. So, from what I understand, I don't have firsthand

knowledge, but from what I understand that Merck supervised and/or conducted toxicology studies.

Q. Okay. And you weren't a part of that. Scripps was not a part of that.

A. Scripps — well, I'm not sure if Friedlander had something to do with it. It's possible Dr. Friedlander had some involvement there, but I myself did not have anything to do with the toxicology.

Q. Pharmacokinetic studies have been performed by Merck in connection with this particular compound, correct, EMD 121974?

[2202] A. They did, in part, with our assistance. We provided them with bleeds from animals at various times. So in some cases we worked together on that.

Q. But those studies were conducted by Merck, correct?

A. Well, it was a combination. We had — I'm sorry — it was simply a combination, for example, if we performed an experiment, we would bleed the mouse, take a small blood sample from the mouse at various times, or the chick embryo or whatever it might have been, and then send that back to Merck for analysis.

* * *

[2204] * * *

Merck, there was a provision for Scripps' testing of compounds submitted by Merck. Do you recall that, sir?

A. I recall there was some discussion about that, correct.

Q. And it's, I think I asked you about this before, and we confirmed that there was an agreement that Merck would — that Scripps would test up to a hundred different compounds provided by Merck?

A. Well, that was originally suggested, but it turned out that we obviously only did no more than 10 to 15. We got some of those from Dr. Nicolaou, but the total amount was in that — it was less than 20. So, as it turned out, in the three-year period of time, from '95 to '98, that's all we looked at.

Q. But when you received those 20 compounds from Merck, you tested them blind, didn't you?

A. That's not accurate. Like I said, several of those compounds came from Dr. Nicolaou, and I think I probably recalled getting a total from Merck of less than 10. So if we consider Dr. Nicolaou gave me five to six, and I tested 15, but [2205] no more than 20, then we're talking about considerably less from Merck. So let's say 10, perhaps 10 compounds total.

* * * *

[2223] Q. By the way, if you were just starting basic research in the middle of 1995, could you be proposing to begin clinical trials within three years?

A. It would be preposterous to assume for one minute that you were initiating basic research endeavors with the idea that within a three-year period of time you would have a clinical drug. I've never heard of any research basic research project started that resulted in a three-year period of time in clinical trials. In all my years I've never heard of such a thing. So I would have never assumed that a basic research project would have led to a clinical entity in three years.

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APPENDIX 46 — TRIAL TESTIMONY: RE-DIRECT EXAMINATION OF DEFENDANT DAVID A. CHERESH, PH.D., SENIOR SCIENTIST AT THE SCRIPPS RESEARCH INSTITUTE, CALLED BY DEFENDANTS ON MARCH 2, 2000

[Commencing at page 2223]

Q. By the way, if you were just starting basic research in the middle of 1995, could you be proposing to begin clinical trials within three years?

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APPENDIX 47 — TRIAL TESTIMONY: DIRECT AND CROSS-EXAMINATION OF EXPERT WITNESS LINCOLN BYNUM, M.D., REGULATORY CONSULTANT, CALLED BY DEFENDANTS ON MARCH 2, 2000

DIRECT EXAMINATION

[Commencing at page 2232]

* * *

Q. Are you familiar with the process that a drug sponsor has to go through to obtain FDA approval of a drug?

A. Yes, I am. It's what I've been doing for the last 17 years.

Q. Do you have any particular specialty in this area?

A. My specialty and my role is as a clinical specialist. You might consider that everybody on the project team has a double role. One is as the specialist in their area and their second role is as the member of the team whose helping do the planning. Occasionally that secondary role involves being the team leader. And for some of the project teams I was on, I was the team leader. So everybody sort of wears two hats. You do your own specialty, but then you also participate in the general function and planning processes of the team.

Q. To what extent do you participate in the preclinical planning process?

A. To the same extent as the other team members. Everybody contributes, so that when it's time to plan a preclinical program, there is input from everybody on the team. So that all team members are intimately involved in

the overall planning of the process, including choosing the types of [2233] studies that should be done, the types of animal models or in vitro models that should be done.

Now, the team then — the members of the team then don't actually perform the studies. Once the planning process is finished, then it's the preclinical specialist that actually goes off and runs those studies, actually gives the drug to the mouse and pours the test tubes and that sort of thing.

Q. Have you personally been involved in the planning of preclinical programs?

A. Yes, many times, on the project teams that I've been involved with.

Q. And to what extent have you participated in that planning?

A. To a great extent. I think the two people that — actually I guess the three people that are the most important on the team like that to plan the preclinical program are, of course, the preclinical specialists, but also the clinical specialist and the regulatory specialist. The clinical specialist is important in the planning of the preclinical program because of the fact that the direction in which it goes depends upon what the ultimate clinical use of the drug is going to be — how the drug is going to be used in humans depends upon how you want to study it in animals and what sorts of animal models you want to use. And the same thing is true once the drug gets into clinical testing in humans. The [2234] clinical expert has to be very familiar with everything that was done in the preclinical phase, because all of that data is crucial, is essential, to the planning of clinical programs. You have to know what the drug does in animals before you know what it's likely to do in humans.

Q. So in order to plan the clinical program, you have to understand and rely on the preclinical program?

A. Absolutely.

Q. About how many drug development programs have you worked on over the years?

A. Well, to one degree or another I've been involved in over 40 different programs. As far as the programs in which I've been a project team member and done the types of planning that I've just been describing, that's been seven different programs.

Q. And in those seven different programs, have you worked from start to finish on those programs?

A. Yes.

Q. Now, as a result of all this, do you know the types of preclinical data that are reasonably related to obtaining FDA approval?

A. Yes, I do.

[2233] Q. And to what extent have you participated in that planning?

A. To a great extent. I think the two people that — actually I guess the three people that are the most important on the team like that to plan the preclinical program are, of course, the preclinical specialists, but also the clinical specialist and the regulatory specialist. The clinical specialist is important in the planning of the preclinical program because of the fact that the direction in which it goes depends

upon what the ultimate clinical use of the drug is going to be — how the drug is going to be used in humans depends upon how you want to study it in animals and what sorts of animal models you want to use. And the same thing is true once the drug gets into clinical testing in humans. The [2234] clinical expert has to be very familiar with everything that was done in the preclinical phase, because all of that data is crucial, is essential, to the planning of clinical programs. You have to know what the drug does in animals before you know what it's likely to do in humans.

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Q. And in those seven different programs, have you worked from start to finish on those programs?

A. Yes.

Q. Now, as a result of all this, do you know the types of preclinical data that are reasonably related to obtaining FDA approval?

A. Yes, I do.

Q. Do you do anything to stay current with new developments in the drug approval process?

A. Yes. There are a number of publications that are put out [2235] by publishers in Washington that keep a very close eye on the FDA. And they describe new changes in regulations and changes in guidelines. And we receive those publications in my office, and I review them quite frequently.

In addition, I have attended seminars put on by a company, a group called the Drug Information Association, that tells the participants exactly what are the important regs, regulations, what are the important guidelines, brings the participants up to speed on new changes, new developments in the FDA process.

And certainly every time I sit down with a project team and we do a drug development program, that's an opportunity for everybody to discuss what is the latest thing at the FDA and to actually go back and consult regulations and reread things that we have read many times, just to be sure that we're getting everything right, we have the most recent information. And our regulatory — the regulatory specialist that works for me and my company has the mandate to review data that becomes available through the FDA, primarily through the website on the Internet that the FDA maintains where they publish all new kinds of regulations and information. And she — her responsibility is to summarize those and distribute those throughout the company so we're all up to date on what's going on with the FDA.

Q. Now, you've mentioned that you attend seminars. Do you also prepare and conduct seminars on the FDA approval process?

[2236] A. Yes, I have. I've conducted seminars on FDA regulations and guidelines as well as international guidelines.

MR. ROOKLIDGE: Your Honor, defendants offer Dr. Lincoln Bynum to testify as an expert regarding the process by which drugs are approved by the FDA and the information that is reasonably related to that process.

THE COURT: Very well. Ms. Brennan?

MS. BRENNAN: Yes. Thank you, Your Honor. Actually plaintiffs do want to state an objection on the record under Daubert and Kumho Tire that Dr. Bynum is qualified as a clinical expert, he's not qualified, in plaintiffs' opinion, to testify about preclinical matters relating to the FDA.

THE COURT: Do you wish to examine him any further?

MS. BRENNAN: No, I just wanted to state on the record. Thank you.

THE COURT: I find that he's qualified as an expert in the process of obtaining the approval of the federal — FDA — and the approval of the FDA in the use of new drugs, and that he also qualifies as an expert in the regulations and guidelines which relate to that agency.

Anything else, Mr. Rooklidge?

MR. ROOKLIDGE: Yes, Your Honor. We're also proffering him as an expert in the information that is reasonably related to that FDA drug approval process.

THE COURT: I'm not sure — does that require [2237] expertise?

MR. ROOKLIDGE: Well, I think — I was just trying to get specific. His expertise in the areas you've already mentioned really include that as well, so I don't think we need to necessarily specify that.

THE COURT: Go ahead.

Q. BY MR. ROOKLIDGE: Dr. Bynum, have you been retained by the defendants in this lawsuit?

A. Yes, I have.

Q. And you've been retained to provide expert testimony in this case?

A. That's right.

Q. Have you ever served as an expert witness before?

A. Yes.

Q. How many times?

A. About six times.

Q. Before this case have you been — before this case started, have you served recently as an expert witness?

A. About a year and a half ago.

Q. Is testifying as an expert a large part of your business?

A. No, not at all. As a matter of fact, up until — actually up until I began this case, I had not done any expert testimony for roughly 15 years.

Q. Are you being compensated for the time that you've spent working on this case?

[2238] A. Yes, I am.

Q. Were you asked to form an opinion about whether certain experiments conducted by Drs. Cheresh, Friedlander, Laub and Storgard between 1995 and 1999 were reasonably related to the development of information for and/or submission of information to the United States Food and Drug Administration?

A. Yes, that's what I was asked to form an opinion on.

Q. Have you formed an opinion on that subject?

A. Yes, I have.

Q. What is your opinion?

A. My opinion is that the experiments were reasonably related to the development of information for the FDA.

Q. Were you also asked to form an opinion as to whether the uses of these accused cyclic peptides have contributed either directly or relatively directly to generating the kinds of information likely to be relevant to the FDA process?

A. Yes.

Q. And have you formed an opinion on that issue?

A. Yes.

Q. And what is your opinion on that issue?

A. That the data from these experiments does contribute directly or relatively directly to the generation of data for the FDA.

Q. Can you please describe for the jury the steps that you took in arriving at these conclusions?

[2239] A. Yes. Originally I reviewed the testimony by deposition of the scientists at Scripps and Merck along with some published articles in the scientific literature that were based upon the results of the experiments. I subsequently reviewed laboratory notebooks from the Scripps laboratories that describe the experiments and also had the opportunity to speak with Dr. David Cheresh on three occasions to discuss the studies.

Q. And have you also been listening to and reading some of the testimony in this case?

A. Yes, I have.

Q. Am I correct in understanding from your answer that your analysis has proceeded in stages?

A. That's right.

Q. And have those stages had anything to do with the accusations of infringement in this case?

A. Yes. At each stage I formed my opinion based upon whatever was available in terms of data at that time.

Q. What I'd like to do now is shift gears a little bit. And if we could put up a Demonstrative Exhibit A14. What I'd like to do is have you talk a little bit about the drug development process.

MR. ROOKLIDGE: Your Honor, if I could have Dr. Bynum come down to the monitor, it might be a lot clearer for the jury to see each of these stages as we go through it.

THE COURT: He may do so.

* * *

[2240] Q. BY MR. ROOKLIDGE: Dr. Bynum, could you describe the steps that a drug sponsor must go through from beginning to end to obtain FDA approval to market a new drug?

A. Sure. In the earliest stages of what is frequently referred to as the discovery period, this is the point in time when the drugs are originally synthesized in the laboratory, that is, it's not a drug at that point, it's a new chemical compound that somebody hopes will become a drug that's useful for therapy. And the larger companies really do screen thousands, tens of thousands even, over a relatively prolonged period of time. This really requires sometimes ten years to narrow down the number of candidates, the number of possible drugs by a process of elimination, so that you get down to the point where — this graphic is wrong, you don't

really have hundreds of promising compounds in clinical testing phase, you probably get here and have one or you may have a small number, two, three or four, that are relatively good candidates to progress into the rest of the development phase.

During preclinical testing, this is the period of time [2241] when the in vitro and animal experiments are performed. And we have said here that that is probably, on average, around four years. Sometimes a little shorter or longer depending upon the type of drug that's being tested.

Once that process is finished, then the data that comes from those preclinical experiments are summarized in what's known as an IND application. That stands for Investigational New Drug. The Investigational New Drug Application is submitted to the FDA, and the purpose of that application is to convince the FDA that the drug can now be given to human beings as in the clinical trials. So that once that submission is made, then the FDA has a period of time of 30 days. And at the end of 30 days, if the sponsor hasn't heard anything, they are free to continue, to commence, begin the clinical trials. If within that 30 days, if the FDA disagrees, does not agree that the drug should go into human experiments, then they will issue what's called a clinical hold. And that just means that the sponsor can't start that first human clinical trial until they address whatever deficiencies the FDA has identified in the IND submission.

Once the IND is in effect, that is, once there is no clinical hold or just after that 30-day waiting period, then the clinical trials begin. And this is where you first give the drug to human

beings. That we've estimated here, there is an average of around six years duration. It may be a little [2242] longer or shorter, again, depending upon the type of drug.

During this clinical phase, the clinical stage, let's say, there are three phases. And there is a lot of gray zones and overlap in these phases, but these are the general designations that one who does clinical trials puts on these phases.

The first phase, as you might imagine, is called Phase I. And that's the earliest clinical trial that's done, and it's usually done in healthy volunteers, that is, you pay people to come in and take your drug or be given your drug. And that's done in a small number of people, maybe 20 people. And the purpose of those early studies, that first Phase I study especially, is to establish that the drug is safe in humans. You don't want to give it to a large number of people until you're pretty safe that a few folks aren't going to have serious adverse effects from the drug. Also that's the opportunity to measure some other things, like how fast the drug is absorbed into the body, what sorts of blood levels you get of the drug, and how fast it's excreted, that sort of thing. That's known as pharmacokinetics. We'll talk some more about that.

But at the end of that period of time, if the sponsor is satisfied that they have collected enough data that indicates that the product is effective and safe, it has to be both, then that's the time that the sponsor files what's called a New Drug Application or NDA. After the NDA is filed, currently the [2243] average amount of time that it takes the FDA to review most NDA registrations is approximately a year. At the end of that year, if the FDA agrees that the data from the

clinical trials shows that the drug is effective and safe, then they give the sponsor approval to sell that drug to the public.

Q. Let's go back to the experimental stage. In that stage is the sponsor, or who ends up being the sponsor, in addition to performing experiments, also synthesizing compounds?

A. Yes, that's exactly what this — the initial stages are. And there may be synthesis of new compounds all throughout that experimental phase.

Q. Now, after we leave the experimental phase, can you generally describe what the purpose is of the preclinical phase?

A. Yeah. The preclinical phase is to demonstrate what the drug does basically. And, first of all, you want to know, if it does anything. You want to know if it's going to be a potential therapeutic agent. So you have to show that there is some effect of the drug on some — that you can measure — in some way. And that's usually either doing the in vitro studies that we talked about or the animal studies. And as you've heard people talk about rabbit arthritis, and those are called models, in other words, the rabbit has arthritis that is sort of a model of what it looks like in humans. It's not the same disease, it's a model. So you choose a model and you say, all [2244] right, if it works in the rabbit, that's a drug that may work in people. Then you would decide, all right, now we've got to establish, not only might it work in people, but is it likely to be pretty safe. So then you'd do what are called the toxicology studies or safety studies. And to identify what kinds of adverse effects might happen and to — and to hopefully demonstrate that they are not serious and that —

and that the drug is appropriate to give to a human being. That's a very significant transition. And it's a very heavy responsibility for the FDA to be required to decide, can this drug be given to a human being. Giving it to animals or testing it in the laboratory is no big deal. But once you first give it to that first person, that's a major decision.

Q. Well, let's stay with the preclinical phase. You've talked about the efficacy, in other words, does it do anything, and you've talked about the safety. Are there other aspects of the compound that are investigated in that preclinical phase?

A. Yeah. There are a number of different types of studies that are performed. One is called a pharmacology study. And pharmacology basically is what the drug does to body functions. And this relates to efficacy, because that pharmacologic effect may, in fact, be its efficacy. It may be the effect that you're looking for in treating a disease. They also do pharmacokinetics. Pharmacokinetics, as I mentioned a minute ago, is what the body does to the drug, and that is how [2245] fast it absorbs it, how fast it metabolizes it, how fast it gets rid of it.

Q. Okay. Now, in a nutshell, then, what is the purpose of the IND?

A. The purpose of the IND is, in essence, to convince the FDA that this drug should be used in humans. And that — as I said, that's probably the key part of any drug development process.

Q. Now, when you go past the IND into Phase I, you mentioned that the purpose of Phase I is testing for safety; is that correct?

A. That's right.

Q. And what size of a group is considered in that first test?

A. It could be anywhere from a dozen people up to 25 or 30.

Q. So it's a relatively small group.

A. That's right.

Q. Then what about Phase II, what's the purpose of Phase II?

A. Phase II is the first time the drug, typically, the first time the drug is actually given to patients with the disease you're trying to treat. Remember, we said Phase I is normal volunteers. Phase II are relatively small studies or moderate size studies in which you first give the drug. If you have an arthritis drug, for example, that's the first time you give the drug to people with arthritis. Usually those studies are — [2246] this is kind of what we call proof of concept, is it really going to do something. But you don't give it to a large number of people, because, on the one hand, you're not sure it's going to work, and, on the other hand, you only have a small amount of safety data at this point.

So Phase II usually — these studies are generally done with a placebo. I don't know if you're familiar with that term.

Placebo is like a sugar pill. So you give some of the patients the sugar pill and some of the patients your drug, just to be sure if the drug is going to do better than what is, in essence, no treatment at all.

Q. So is Phase II, then, conducted with a relatively small number of patients?

A. Yeah, probably in the range of hundreds.

Q. Tell us about Phase III. What's the purpose of Phase III?

A. Then the last part of the clinical process is Phase III. And Phase III begins once you have first shown in Phase II that the drug works and that it's reasonably safe. And Phase III is the phase in which you give it to many more patients. This is where you do larger studies to get lots of experience and a much larger range of patients, and also, not only for efficacy, but also to expand your safety experience and to be able to ensure the FDA that in a large number of patients the drug didn't cause any extreme or serious adverse effects.

[2247] Q. Now, do these three phases of the clinical stage ever overlap?

A. Yes, they may. That's why I say that it's not a rigorous progression necessarily. For instance, if something about the drug or the way the drug is administered changes, if the sponsor decides that they want to use a different dose or a different schedule, then they may want to go back to Phase I and test it and make sure that that new dose is safe.

Q. Now, are there ever occasions where the sponsor that's in clinical trials will want to go back and perform preclinical experiments?

A. Yeah. In essence, for the same reason. If something changes about the drug, whether it's the dose or the formulation, there are different ways of manufacturing the drug. If you change the way you make the drug, if you raise the dose, if you decide to give it to a different type of patient, then you may want to go back to the preclinical phase and test those new doses in animals to establish their — that they work and are safe — before you will turn around and give that new dose to a human being.

So really the term "preclinical" isn't very accurate. That sort of indicates that everything here is done before the clinical trials, and it's not true. The FDA has begun using currently the term "non-clinical" more often rather than "preclinical."

[2248] Q. Okay. Now, you mentioned at the end of the clinical trial phase is the filing of the New Drug Application. What is the purpose, in a nutshell, of that New Drug Application?

A. In a nutshell, it's to convince the FDA that the drug is appropriate for selling to the general public.

Q. And what kind of data is included in that New Drug Application?

A. That's data derived from clinical trials in which you treated patients with the disease you intended to use the drug for and to show that it is effective and that it's safe. And

"safe" is a bit of a misnomer. I've heard FDA people say there is no such thing as a safe drug. It's kind of scary, but what they really mean is, there is no such thing as a drug that doesn't have some side effects. Every chemical you put in your body is likely to have, not only the positive effect that you're looking for, but you're likely to have side effects. If you take an aspirin for your headache, maybe some of you have noticed that sometimes you get a stomachache, because aspirin is irritating to the stomach. So every drug has some side effect. So when you say safe, just keep in mind that that's a very relative term. It's not absolute. Drugs are not safe or not safe — they are relatively safe.

Q. Let's go back to the NDA. Does the NDA ever include preclinical data?

A. Yes, it does. As a matter of fact, the NDA is intended to [2249] be a fairly exhaustive description of what's known about the drug. And, particularly, if the preclinical data is revealing in terms of how the drug works in terms of certain pharmacological properties of the drug, they may be included in the NDA. And, in fact, the NDA calls for, in one of its sections, so it's not a choice, you have to put the animal pharmacology data into the NDA.

Q. And is that because the NDA is the document that's going to serve as the basis for whether the FDA ultimately approves or disapproves the drug?

A. That's right.

Q. Now, for drugs that ultimately get to the market, by which I mean go on sale to the public, how long does it

typically take to complete the drug approval process or the drug development process?

A. As the drug development process, as we have indicated here, which starts with the preclinical testing and goes through the clinical tests, takes about — we have indicated 10 years. The latest estimate says that it may be as long as 12 years on average.

Q. Now, when in that 10- or 12-year process is the first point at which both safety and efficacy of the drug is established in human patients?

A. The first time that you can have a result that indicates safety and efficacy is in the — is at the end of Phase II, [2250] when you first treated the patient population for which the drug is intended.

Q. Now, we've talked about marching through this process from beginning to end, but can, in fact, the drug sponsor fail at any of these stages?

A. Oh, absolutely.

Q. So, for example, if the drug sponsor gets to Phase I and there are serious adverse side effects, what happens?

A. That drug is dead. Basically the current statistics that come out of a group at Tufts University called The Center for Drug Research is that for every one drug that finally gets approved at the end of the FDA review, it takes ten thousand drugs to go into the process at this end. So one in ten thousand makes it to the end. When you get to the FDA — excuse me — to the IND stage, then it's something like one in five. So

there is a lot of things that can happen along the way. You can find in the preclinical stage that you have a lot of mice that are dying or getting very sick. You will drop that drug. In the clinical stage, you may find, first of all, that it doesn't work as well as you thought it was going to, you're not likely to want to market that drug, or it may have safety problems. It may have more side effects than you think or that the FDA thinks are justified by the therapeutic effect.

Q. Now, can a sponsor who wants to conduct drug studies in [2251] the U.S. just skip over any one of these phases from the IND to Phase I, Phase II, Phase III?

A. Not at all. The IND is absolutely essential to do drug trials in the U.S.

Q. So could a sponsor come in and say, I've done some clinical trials in Europe and I want to do trials in the United States, can I just skip the IND?

A. No.

Q. Are European trials the equivalent of a U.S. IND?

A. No, they are not.

Q. Are European trials on one indication the equivalent of a U.S. IND on other indications?

A. No.

Q. Okay. And by "indications," what are we talking about here?

A. We use the term "indications," and that is sort of an FDA term. That means a disease, that is, arthritis is an indication, high blood pressure is an indication. So the word "indication" really translates into whatever disease condition you're treating.

Q. And if a sponsor performs trials in Europe, will the FDA automatically accept data from those trials as a substitute for data from U.S. trials?

A. Not automatically.

Q. And who makes —

[2252] THE COURT: Just a minute.

MS. BRENNAN: I wanted to interpose an objection that he's going beyond what he disclosed in his expert witness report.

MR. ROOKLIDGE: Your Honor, this is just foundational describing the FDA process.

THE COURT: I'll allow it for that purpose.

Q. BY MR. ROOKLIDGE: The question was, if the sponsor does trials in Europe, will the FDA automatically accept data from those trials as a substitute for data from U.S. clinical trials?

A. No.

Q. Okay. And who makes the decision about whether European data may be adequate for U.S. regulatory purposes?

A. That's the FDA decision.

Q. And when does the FDA make that decision?

A. At the point in time when they are reviewing the NDA.

Q. Why don't you go ahead and sit down. I think we can take a break from this exhibit for a moment.

You mentioned some terms here. Let's make sure that we've got these terms down. You've talked about safety data. Is that the same as toxicity data?

A. Yes, or toxicology data.

Q. And, in a word or two, what does toxicity data show?

A. It shows the unwanted or adverse effects of a drug or [2253] chemical.

Q. Okay. And does the toxicity data that's developed in the preclinical testing period prove that the drug is going to be safe in humans?

A. No, it doesn't. It can only provide an indication.

Q. And you also used the term "efficacy," am I correct, and that's the term for does it work?

A. That's the term for does it work.

Q. And then you used the phrase "chemistry and manufacture"?

A. And that's how the drug is produced or synthesized.

Q. And how about "mechanism of action"?

A. That is how does the drug work.

Q. "Pharmacology"?

A. That's the effect of the drug on the body.

Q. And "pharmacokinetics"?

A. That's the effect of the body on the drug.

Q. Now, you mentioned briefly that Tufts study about the uncertainties in the process. Would you characterize the FDA drug approval process or how would you characterize that process in terms of complexity, costs, and difficulty?

A. I think we have already had — I've already given some indication of the fact that it's very lengthy. Just the drug development process itself is over a decade and very costly as we've seen — that Tufts Center for Drug Research Study established that the average cost to bring a drug from the [2254] early synthesis through to an NDA filing is something like five hundred million dollars.

Q. Five hundred million for each drug?

A. That's right.

Q. And you mentioned briefly the statistic, let's see if we can get that up on the screen again. Do you understand that this is the same study that the plaintiffs' damages expert, Dr. Anderson, is relying on?

A. Yes, I'm sure it is.

Q. And these were the numbers that you talked about generally. Could you briefly explain how those numbers work?

A. Yeah. As we see, of the five or ten thousand that are screened originally in the experimental phases, one is likely to make it to FDA approval. In the preclinical stage, you rapidly — actually by the time the preclinical stage arrives, you've whittled your number of candidates down to, I'm sure, less than 250. And probably by the time you get into the preclinical stage, you're down even lower than those numbers indicate. You're probably down to four or five at that point. And then to get into the clinical stage, that's where you choose a single drug to go into drug development. And then of those — of the five that go into clinical research, one gets approved.

Q. So what do these numbers say about the level of predictability in the FDA process?

[2255] A. Well, it says that you don't have a lot of predictability. There is a lot of uncertainty. And if you're going to spend five hundred million dollars, you're taking a big gamble if only one in ten thousand is going to make it, if only one out of five that goes into clinical research is going to make it. And there is a lot of reasons for that unpredictability.

* * *

[2258] * * * hasn't shortened the process. And, in fact, as the statistics come out, the duration of that drug development program is getting longer instead of shorter.

Now, why is that? It's because, although the FDA is doing all this communication, they are also requiring more data. They are coming under a great deal of scrutiny and a great deal of criticism for two things — one is not getting drugs approved fast enough, you know, particularly from the AIDS community, you hear people say get this drug approved, people need it, people are dying. And if they respond to that and approve the drug quickly, then what are they criticized for? It's not safe, they didn't give it a full review. So they are torn in two different directions. And they have been criticized widely. There have been a number of drugs taken off the market after the FDA approved it in recent years. I'm sure you're all aware of that. When that happens, the FDA gets blasted, not only by the public, but by Congress. So they are getting more and more careful. They know they have to know more and more about the drugs they are approving. And so they are demanding more and more information from the drug companies all along the whole process of developing that drug, because it's a heavy, heavy responsibility. I have tremendous [2259] respect —

THE COURT: What was your question, Mr. Rooklidge?

Q. BY MR. ROOKLIDGE: Well, let me go on with my next question. You mention they are asking for more information. Isn't the FDA trying to cut down on the amount of paperwork?

A. Well, they would like to cut down on the amount of paperwork. Everybody would like to get rid of paper, and that's why we live in a computer age and a technological age. And the FDA is moving relatively rapidly toward being able to accept and being able to deal with sponsors purely on an electronic basis. So that, instead of sending a truckload of paper in when you file your IND or your NDA, you can send it all in by computer. That day isn't here yet. There are a few companies that have done that, but it's not universal, by any means. And that's the major effort to cut down paperwork. But because of their increasing needs for data, they are having a real hard time actually making a dent in the amount of paper that they have to deal with.

Q. Well, despite these efforts to improve the process, have you recently heard from anybody at the FDA about the predictability of the process?

A. Yes. One of the — a high-level staffer there was taking part in a teleconference sponsored by the FDA, and he characterized the regulations as flexible and requiring a lot of, quote, judgment, just indicating that, in fact, even the [2260] regulations don't give you a lot of good information. And we'll talk more about regulations in a little while.

Q. Is that statement borne out by your experience?

A. Yes, it is.

Q. Let's talk about the consequences of this unpredictability for the drug sponsor. Are the implications of this variability in the process with a drug sponsor?

A. Well, sponsors have to — have to take into account the fact that they can never be assured what they are doing is going to be successful. And the FDA makes a big point of that. The FDA will tell a sponsor, all right, here are the studies that I want you to do in order to gain approval or in order to have your IND or NDA approved. But they will never say, I guarantee that, if you do these studies, that you'll be approved. And that's because of the fact that they know things may change. For that reason, if a sponsor wants to hedge their bet, if anyone is a gambler, that means you do a little extra in order to be sure that, when you get to the end of the process, you're going to have enough data and the right kind of data that will be persuasive to the FDA.

When I worked at Syntex, the term that was used there was the belt and suspenders approach — you did a little more than you thought you absolutely have to do. And there are several reasons for doing that. One is scientific research is unpredictable. You never know, when you start a study, if it's [2261] going to work or not. And we can even see that in this program. There are some of the animal models that didn't show any effect of the drug. And you never know when that's going to happen. So if you only start the very basic minimum number of studies that you think you're going to need, some of them may not work out the way you want them to. So, generally, the belt and suspenders approach is that you do a little more than you think is absolutely necessary just to be sure that you've covered the bases.

Q. So in terms of the drug development process, that means that, in this preclinical testing period, the sponsors are doing a lot more?

A. I think the sponsors are doing what they think will provide enough data, but more than enough data for the FDA, so that they are absolutely sure, when they get to that IND stage, that the FDA is satisfied by what they see.

Q. And the way to satisfy the FDA is to — by submitting a lot more data?

A. Well, yes.

Q. Now, does the FDA limit the amount of data that a drug sponsor can submit?

A. No, they don't. In fact, in the regulations they talk about filing of an IND. There is a segment in the regulations that says, I'm not going to quote it exactly, the FDA expects the sponsor to use considerable discretion as to what kinds and [2262] how much data are put into the IND. So, basically, that's up to the sponsor. If they want to — whatever the sponsor wants to put in an IND or an NDA application, that's their choice.

Now, generally, the conversations with the FDA will help to determine what that is, but it's ultimately the sponsor's choice.

Q. And does the unpredictability of the process inform that discretion of the drug sponsor?

A. Yes.

Q. And how so?

A. Well, it indicates that the sponsor probably wants to overdo it a little bit and do a few more studies than are

absolutely necessary. And the other thing about the scientific process is, there is nothing that's black or white about it. You don't have — you don't have a clear win or a clear loss in many instances. You have a result that looks pretty good. And if the sponsor looks at it, they may say, looks good enough to me. But the FDA may look at it and say, not quite good enough. So you frequently have to have back-up data. If it looks pretty good, the FDA thinks, well, maybe that was just by chance. If you got another study that verifies it, then that's a good deal more convincing to the FDA, and the fact that it's a real result and it's important enough to approve the drug.

Q. Do you know who Gerald Meyer is?

A. Yes.

[2263] Q. Who is Gerald Meyer?

A. He's a former FDA staffer.

Q. And do you understand that he's been retained by the plaintiffs in this case as their FDA expert?

A. Yes.

Q. Okay. And did you read his testimony regarding only doing the bare minimum preclinical experiments required to get approval?

MS. BRENNAN: Objection, that misstates his testimony, assumes facts not in evidence.

MR. ROOKLIDGE: I can restate that, Your Honor.

Q. BY MR. ROOKLIDGE: Did you read Mr. Meyers' testimony?

A. Yes, I did.

Q. And did you understand his testimony to suggest that drug sponsors should only do the bare minimum preclinical experiments required to obtain FDA approval?

A. That's the general gist of his recommendation.

Q. Do you agree with Mr. Meyers' testimony?

A. No, I don't.

Q. And why not?

A. For all the reasons that I've explained, that I think drug sponsors need to provide the FDA with as much data as they can for those two overriding reasons. One is, the FDA wants to participate in the whole process. They want to know everything there is to know about a drug. Because when they approve that [2264] drug, they better be able to go back and say, you know, if something goes wrong, they better be able to say this is what knowledge of it. And I'm sure that, if you were that first patient in that first study, I'm sure I would, I'd want to know that, when the FDA approved that drug for use in humans, that they knew everything there was to know about the drug, that they had no question in their mind that this was an appropriate drug to be given to people. By the same token, if you're a patient and your doctor is writing you a prescription for a drug, I think you want to know that the FDA, when they approved it, they knew that drug backwards and forwards. And the FDA is the same way. They don't want

to stick their neck out and approve drugs for use in humans without knowing fully what they are doing, what they are approving.

Q. Now, is this bare minimum approach one that you have ever seen in your 17 years in the pharmaceutical industry?

A. I've never seen that, no.

Q. Is it practical to design a program using this bare minimum approach?

A. I don't think so. It's not — it's not only not practical from the FDA standpoint, but it's not practical from the standpoint of the sponsor. Obviously the sponsor wants to know everything that they can about the drug, so they know exactly where it's going to be used, and they can provide that [2265] information to the FDA, because the sponsor wants to get meaningful feedback from the FDA. And if they don't tell the FDA what the drug's all about, the FDA can't function then as that consultant we talked about. They can't actually participate in the decisions that the sponsor has to make to develop the drug.

Q. Does the FDA publish any kind of guidance for sponsors?

A. Yeah, there are several levels of direction that the FDA gives to sponsors. The highest, I suppose you'd say, or the most binding level, is the law. And there is a law called the Food Drug and Cosmetic Act passed by Congress. And that law is fairly general.

So the FDA has written what they call regulations. Regulations are a description of how drug sponsors should follow the law, how they can implement the law. So it's a bit more detailed. It's a bit more functional. But even the regulations are very general and nonspecific, and they don't give specific instructions on how to develop a certain drug, for example.

So the next level of communication is what the FDA calls a guideline, and a guideline is not binding. The law and the regulations are. You have to do what the regulations say. You don't have to do what the guidelines say. They are an — they are an effort to further interpret the regulations, to give a little bit more detail and a little bit more description of [2266] what the regulations are calling for. But even the guidelines aren't specific and can't tailor guidelines or regulations for every drug that's likely to come along. So they are, by nature, rather general and nonspecific.

Below that there is a level of communication that's known as guidance. Guideline guidance. The guidances are usually a question and answer process. And that's when a sponsor will read a guideline and then say, I still don't quite understand, and they will fire questions back to the FDA. And then the FDA will publish a list of all the questions they receive with answers. Even the guidances, though, aren't very specific for a certain program.

So the final level of communication is what we've talked about, that's that person-to-person interaction with the company talking specifically about the program that that

company is undertaking. And that's the only way to really get specific information from the FDA to the drug sponsors.

Q. So does the sponsor — the sponsor sits down with the statute and the regulations and the guidelines and the guidances, does the sponsor have every piece of information that that sponsor needs to get that drug through the FDA?

A. Not at all. Personal communication is the most important part.

Q. Okay. Now, you've talked a little bit about the vagueness in the statute, the regulation, the guidelines, the guidances. [2267] Give us an example of what kind of vagueness you're talking about.

A. One example is actually in the GLP regulation. When it talks about the kind of animal data that the FDA wants, it says, and, again, I'll try to quote it, the sponsor should provide adequate toxicity data from animal or in vitro studies.

Now, I personally couldn't go out and design a preclinical program with that kind of instruction. What's adequate? How many animals? What kind of animals? How do I treat them, et cetera? Even the guidelines — then the guideline comes along to help make that a little more specific. And the guideline says, as to mammalian species, one should be a non-rodent, that is, you can't have one be a mouse with the other should be something else. But still you're left sort of wondering what species are the most appropriate, which ones will give me the best information for the FDA. So that's the point in time when you have to sit down with the FDA or get them on the phone and say, let's talk about this, what shall I really be doing.

Q. Let's talk about these pre-IND communications. Let's go back to the preclinical stage. Would you describe for us in a little more detail how these face-to-face meetings or these person-to-person meetings come about in this preclinical phase?

A. It's at the instigation of the sponsor, generally. And [2268] the sponsor will notify the FDA either by phone call or a letter that they are developing a product and they would like to interact with the FDA. Generally that's done, not right at the beginning, not right when you first start the process, because you want to have at least enough information that the FDA can make intelligent decisions. So you want to wait until you've developed some data, you have a little bit of background, and then establish that first meeting with the FDA. That's when the planning process begins. You say, here's the data we have, here's what we plan to do, how would you change this. And those — and those meetings can be every month or two. They can be — I've had some sponsors that have interacted with the FDA as often as once a week over a period of over a year.

Q. And do these meetings have to be face-to-face?

A. No. Most of them are by telephone. Generally there is, if you — if your preclinical program is lengthy, you might have a face-to-face meeting once every six months or a year, and the intervening meetings are by teleconference.

Q. And how many meetings are there typically through this preclinical period?

A. Well, as I said, it's quite variable, and it depends a lot upon the reviewer at the FDA. Some reviewers are very

responsive. Some reviewers, as I say, actually are calling the sponsor instead of the sponsor calling them saying how's [2269] everything going and asking for data, send me your — send me more information. Other reviewers are a little bit more standoffish and you have to call them. So it can vary anywhere from once — once every two or three months to, as I said, once a week.

Q. And are there any regulations that dictate how many meetings there have to be?

A. The regulations provide for only one meeting, and basically what the regulations say is that, if the sponsor requests a pre-IND meeting, the FDA has to honor that request once.

Q. And, as a practical matter, is there ever just one IND meeting, pre-IND meeting?

A. Well, I suppose there could be, if you have — if you have a very, very simple drug or an old drug that has been around for a long time, you know, and you're going to use it for something new. Like if somebody wanted to do something new with aspirin, or, you know — a drug that's very, very familiar and that doesn't require a lot of new data. I would say maybe one pre-IND meeting would be sufficient in that case.

Q. In the last ten years of your experience have you been involved in a preclinical program with just one pre-IND meeting?

A. No, because I haven't — I don't think I've been involved in any programs that have that simple and basic of drug.

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[2286] * * *

Q. In your experience does this preclinical stage ever [2287] include experiments where the lead drug candidate is compared to other drug candidates?

A. Yes, it does.

Q. Okay. And in these kinds of experiments, are they reasonably related to the development of information for the FDA approval process?

A. Yes, they are.

Q. And why is that, briefly?

A. Well, because, obviously, if you change the lead drug that you're going to file and you can establish why you've done that, by showing that one drug is better than another, that's information that's basic to why you're developing this particular drug for submission to the FDA.

Q. Okay. And if we could have a timeline back up again. In the preclinical stage, the drug candidate can change?

A. Oh, yeah.

Q. And in the clinical phase, can that drug candidate ever change?

A. Sure.

* * *

[2287] * * *

Q. Does the fact that an experiment is repeated, meaning it'sperformed more than once, mean that that experiment, the first experiment, is not reasonably related to developing information or data for the FDA?

A. No. And there is a general principle in science that, one positive result doesn't definitively establish a successful [2288] drug. One positive result could be a fluke. It could just be an accident. It happened to get a good effect. So, generally, in clinical science, in preclinical and clinical science, one wants to confirm any good result. So even if you do a study twice, it doesn't mean the first one wasn't reasonably related.

Q. Earlier you testified that in your opinion the experiments that you considered were reasonably related to the FDA process. When did you first arrive at this conclusion?

A. After reviewing the testimony of the scientists that had conducted the studies.

Q. And did you receive more factual information as time went on?

A. Yes, I did. The original information that was provided to me, as I indicated, was testimony by the scientists, accompanied by some published papers.

Q. Now, Dr. Cheresh, you saw yesterday, had a big chart where he went through and identified all the experiments. Did you review all those experiments on that chart?

A. Yes, I did.

Q. Okay. Now, let me direct your attention. There was one experiment on there directed to MMP2. Did you consider that?

A. No, I didn't.

Q. Okay. So with the exclusion of the MMP2 experiments, it was your conclusion that all of the rest of those experiments [2289] were reasonably related to the FDA process.

A. That's right.

Q. Did you consider any experiments conducted prior to 1995?

A. No.

Q. Have you reviewed the testimony of Dr. Storgard and Friedlander about their proceedings or their reasons for conducting the accused experiments?

A. Yes.

Q. Okay. And did you also listen to Dr. Cheresh testify yesterday and today about his reasons for conducting his experiments?

A. Yes, I did.

Q. In your opinion are the judgments that Dr. Cheresh and Dr. Storgard and Dr. Friedlander made about the information or data that they would get from those experiments reasonable?

A. Yes, they were very reasonable.

Q. Has anything that you have heard or seen in this trial in any way changed your opinion that all of these experiments that you considered, that is, all of the experiments except for the MMP2 experiments, are reasonably related to the FDA process?

A. Nothing has changed that opinion.

Q. Thank you.

MR. ROOKLIDGE: I have no further questions, Your Honor. Although at this time I would move to enter into evidence exhibits AN, WP, CP, AAP, and AAQ.

[2290] MS. BRENNAN: No objection, Your Honor. But there is a question about some of the numbers on one of the exhibits, but that's ministerial.

THE COURT: Very well. Identifications have been offered and will now be received into evidence and may be so marked.

MR. ROOKLIDGE: Thank you, Your Honor.

THE COURT: Ms. Brennan.

CROSS-EXAMINATION

Q. BY MS. BRENNAN: Good afternoon, Dr. Bynum.

A. Ms. Brennan.

Q. Can you tell us, what is the drug at issue in this case?

A. There are several drugs at issue in this case.

Q. Okay. What several drugs are those?

A. Those are the compounds known as EMD 66203 and the — EMD 66203, EMD 85189, and EMD 121974.

Q. All right. Thank you. And can you give us a brief description of what those drugs are?

A. They are cyclic peptides.

Q. Can you tell us anything about the amino acid structure of those drugs?

A. Well, the key amino acid structure is described by the description RGD. Those letters stand for arginine, glycine and aspartic acid.

Q. And what division at the FDA would oversee an application [2291] for a drug such as the RGD drugs you've just testified to?

A. Well, that depends what indication is being filed, is being sought. If the initial indication in this case is a form of cancer, it would be the oncologic drug division.

Q. All right. And are you familiar with the antibody LM609?

A. I've only heard it mentioned here.

Q. Do you know what division at FDA would be in charge of overseeing approval of LM609?

A. Well, since it's an antibody, it would probably be the biologics division instead of the drugs division.

Q. And are there different requirements that apply to biologics versus drugs?

A. Not fundamentally. The biologics are subject to the same IND regulations as drugs are. The major — well, there is a fundamental difference actually. Biologics, the purview of FDA over biologics was established by a different law, a different act, than that for drugs. But, in essence, those laws have both been interpreted by the regulations in the same way. So, particularly, for IND, the same IND regulations apply to biologics.

Q. Do you recall I took your deposition back on July 8, 1997?

A. Yes.

Q. All right. And I apologize, we're going to have to come back to that. Dr. Bynum, have you ever designed preclinical trials?

[2292] A. I've not designed the trials themselves, but I've designed preclinical programs in conjunction with other members of project teams.

Q. All right. Would you agree that your specialty is in clinical as opposed to preclinical studies?

A. That's right.

Q. And have you ever published any articles in peer review journals?

A. Yes.

Q. Do any of those publications relate to preclinical studies?

A. No.

Q. Have you ever conducted statistical analyses relating to preclinical data as opposed to clinical data?

A. My company has not, no.

Q. Is one of the functions of your company data management?

A. That's right.

Q. And have you ever used your data management for clinical as opposed to preclinical data?

A. We use it for clinical data, not preclinical.

Q. Now, if a client of your firm wanted to design a preclinical study, would you subcontract that work or would your company do that work itself?

A. Our company would do that work with the assistance of a subcontractor who is a specialist in preclinical. So that that [2293] subcontractor would become part of the project team, which would include myself and other members of my company.

Q. All right. You would have to go outside your company, though, to bring in some expertise relating to the preclinical trials; is that right?

A. I would have to bring in a preclinical specialist, yes.

Q. Now, Mr. Rooklidge asked you about some opinions you reached earlier in this case. Do you recall that?

A. Yes.

Q. Do you recall when you reached some opinions in this case relating to whether work done by Scripps scientists was reasonably related to the FDA?

A. I think my first opinions were reached in sometime in 1997.

Q. And do you recall you submitted a declaration at that time?

A. Yes.

Q. And do you recall what opinion you reached back in 1997?

A. Yes. My opinion was that the experiments were reasonably related to the information for the FDA.

Q. All right. And back in 1997, first of all, the declaration you submitted, that was under penalty of perjury, correct?

A. That's right.

Q. And how much work had you put in at that time on the case [2294] before arriving at your conclusion that the work being done by the Scripps scientists was reasonably related to the FDA?

A. I had reviewed the testimony of the Scripps and Merck scientists and the accompanying published articles.

Q. Okay. I'm sorry. I asked you how many hours you had spent before reaching your conclusion back in 1997.

A. I'm afraid I can't remember that.

Q. Dr. Bynum, I'm going to hand you a transcript from the deposition taken in July 8, 1997 to refresh your recollection. If you can read down here at the bottom of page 17 starting at line 25 and then up through 18, line 7.

A. You asked then how many hours have you spent in connection with this matter, and I said, "I don't know. We keep our time on a computerized system, and I have a business manager that adds it up at the end of the month. And I haven't seen those totals."

Q. Can you read the portion where you estimated the amount of time you had spent on the case?

A. Do you have an estimate at all? And I said maybe five or six, maybe seven or eight, something like that hours. And then I said, yeah, it may be more than that, but it's hard for me to estimate.

Q. First, I'm going to be handing you what has been marked Plaintiffs' Exhibit 701. Will you please identify what this exhibit is?

[2295] A. This is my declaration which was evidently received by you in May of 1997.

Q. Can you turn to page 5 of the declaration? Is that your signature there?

A. Yes.

Q. And what date did you sign this declaration?

A. May 19th, 1997.

Q. Now, can you turn to page 3 of the — actually, first of all, can you turn to the front page of the declaration and explain for the jury in what — what your declaration was submitted for, the purpose of it?

A. In support of defendants' motion for partial summary judgment.

Q. Under 35 U.S.C. 271(e)(1)?

A. Yes.

Q. All right. So you were asked to give an opinion about whether Scripps research activities were reasonably related to the FDA; is that right?

A. That's right.

Q. Okay. And at that time you estimated you had spent between maybe five or eight hours in reaching your conclusions?

A. Right.

Q. And then can you turn to page 3, paragraph 7? Can you read paragraph 7 into the record, please? [2296]

A. "I have reviewed the declarations of Drs. Cheresh, Friedlander, Finke, Jonczyk, and Goddard submitted in support of the pending motion. In addition, I have reviewed the exhibits attached to those declarations. Based on the factual statements in those declarations and the attached exhibits, I conclude that all of the activities undertaken by the defendants with respect to the Merck cyclopeptides are reasonably related to the development and submission of data to the FDA. My opinion is that the defendants' uses of those compounds have contributed and will continue to contribute directly to the generation of information necessary for FDA review."

Q. All right. At the time you reached this opinion, had you seen any of the data generated by the Scripps scientists listed here in paragraph 7?

A. As I said, I saw their description of their studies and the data that was published in the scientific journal.

Q. Had you conducted any independent review at that time of the data to determine for yourself whether the data generated by the scientists was reasonably related to the FDA?

A. There was nothing made available to me that I could use for any additional study or evaluation.

Q. Well, did you ask defendants whether you could see any materials in connection with reaching your opinion stated here?

[2297] A. I was told that what they provided me was all that — was all that they had, all that was available.

Q. All right. Do you recall in your deposition that I took of you on July 8, 1997 I asked you to describe what a CAM assay is? Do you recall that?

A. Yes.

Q. And were you able to describe what a CAM assay was?

A. I don't remember.

Q. Okay. Can you look at page 27 in the transcript up there?

A. Okay.

Q. For the record, that's the transcript from the July 8, 1997 deposition of Dr. Bynum. I believe page 27 at line 20, right. Can you read that question and answer, please?

A. Can you describe for me, then, what a CAM assay is? And I said, no, I couldn't.

Q. And then could you turn to page 28? And can you read the question and answer starting at line 10?

A. Do you know what CAM stands for? No, I don't. Are you familiar with any of the procedures involved with the CAM assay performed by Dr. Cheresh? The answer is, not the details of the procedures.

Q. Okay. So at the time you reached the opinion here that all the Scripps scientists' research was reasonably related to [2298] the FDA, you were not familiar with what a CAM assay was; isn't that right?

A. That's right. It was not described in the materials that I had reviewed.

Q. All right. Well, didn't you think you should ask what the CAM assay was before you reached the conclusion that Dr. Cheresh's work and the other Scripps scientists' work was reasonably related to the FDA?

A. I was told that there was no additional information that I could request at that point in time.

Q. And who told you that?

A. It's the impression I got from the lawyers that provided me with the data.

Q. Also back in 1997 do you recall that you were asked where the toxicological studies were conducted in connection with the RGD drug compound?

A. I don't recall that query.

Q. Did you testify that the toxicological studies on the RGD drug were conducted at Merck?

A. I may have. And that's my impression today.

Q. What is that? What is that impression?

A. That Merck was to be the one to perform the GLP toxicology studies.

Q. Well, what about putting GLP aside for the moment, in 1997, had you seen any results of toxicology studies by Dr. [2299] Cheresh?

A. No, at least nothing that was a formal toxicology study.

Q. I'm going to read from your testimony at page 56, line 23.

Can you verify whether or not Dr. Cheresh ever conducted any experiments relating to toxicological analysis?

Answer. No, I can't, except by his statement here. I didn't see any results of any toxicology studies.

Do you also recall back in 1997 I asked you whether Dr. Cheresh's description of work he began for Merck in 1989 was related to FDA? Do you recall that?

A. I think so, yes.

Q. All right. And do you recall what you answered?

A. I believe —

MR. ROOKLIDGE: Objection, Your Honor. This is beyond the scope of direct. This witness testified that he didn't consider any experiments before 1995.

MS. BRENNAN: That's for his current expert witness report. I believe I'm entitled to explore with this witness what his opinions have been.

THE COURT: I'll allow the question.

MS. BRENNAN: Thank you, Your Honor.

THE WITNESS: I don't recall what my answer was.

Q. BY MS. BRENNAN: Okay. I'll show you what is — starting at page 61 of the transcript. Again, this is still the July 8, [2300] 1997 — starting right there, line 17, page 61, start there and then review through page 62.

A. Starting at line 17?

Q. Right.

A. Let me have your re —

Q. Why don't you read it to yourself and then see if that refreshes your recollection. You can skip over the objections.

A. Okay.

Q. So do you recall, then, when I asked you with respect to a statement in Dr. Cheresh's declaration that, beginning in 1989, Merck began to provide me with small samples of peptides for my experiment. Upon receiving the peptides, I tested them, A, for the potency of inhibitory effect on integrins, and, B, for the specificity of inhibitory effect for a given integrin.

And then I asked you whether that work as described by Dr. Cheresh was reasonably related to the FDA. And do you recall what your answer was?

MR. ROOKLIDGE: Objection, Your Honor. This is both now beyond the scope of direct and totally lacking in relevance. Ms. Thayer at this point in the deposition objected saying we haven't asked this witness for his opinion about activities that occurred before 1995, and today we have not asked this witness about his opinion for activities that occurred before 1995.

[2301] THE COURT: How was this placed before the witness at that time, at the time of the deposition?

MS. BRENNAN: I'm sorry. How was it placed?

THE COURT: Yes.

MS. BRENNAN: There was a declaration of Dr. Cheresh that had been submitted, and I was having — I was asking his opinion about whether the research being described by Dr. Cheresh was reasonably related to the FDA.

MR. ROOKLIDGE: A fact that he was neither asked to opine on then or now.

MS. BRENNAN: Your Honor, this goes to this witness' basis for saying at any given point in time when a given experiment is reasonably related to the FDA. The defendants want to shut it down in '95, but I think we're entitled to get his opinion on what he thinks about the research done earlier.

THE COURT: I'm going to overrule the objection. Mr. Rooklidge, you will have a full opportunity to inquire of the witness on your redirect.

MR. ROOKLIDGE: Thank you, Your Honor.

Q. BY MS. BRENNAN: All right. And you answered — do you recall what you answered?

A. I said the experiments that Dr. Cheresh is describing would be reasonably related to information for the FDA. And my response at the time was not time dependent. In other words, when he described the experiments that he did with those — [2302] with the peptides, and you asked me if they were reasonably related, I wasn't answering for 1989 or any other time. I was just answering to his description of the experiments.

Q. Right. And Dr. Cheresh had said that that work, as he described, began in 1989; isn't that right?

A. It began in 1989, but he doesn't say that he didn't do it beyond 1995. I was only saying that those experiments as he described them would be reasonably related. I wasn't

intending to say that they would be related if they were done in 1989 or 1992. I just said those experiments would be reasonably related. And I think he continued to do those types of experiments throughout the course of the development of the peptides.

Q. All right. But Dr. Cheresh had declared that, beginning in 1989, he conducted certain experiments and got certain information; isn't that right?

A. Yes, beginning in 1989. He didn't say in 1989.

Q. Right, beginning in 1989. And it's your opinion that, as the experiments as described by Dr. Cheresh, that he began in 1989, were reasonably related to the FDA; isn't that right?

MR. ROOKLIDGE: Once again, Your Honor, we have not asked this witness to opine on any experiments conducted in 1989.

THE COURT: I understand. You will have a continuing objection. [2303]

MR. ROOKLIDGE: Thank you.

Q. BY MS. BRENNAN: Do you need the question reread?

A. As I said in my — my response was that the experiments that he described would be reasonably related. I didn't say when. I mean, if he began them in 1989 and they continued past 1995, that — as I said, my answer was relatively time independent because those experiments

continued throughout the whole course of the development process of the peptides.

Q. All right. But, again, if Dr. Cheresh stated truthfully that he began experiments in 1989, as he described, and you opined that they were reasonably related to the FDA, that is still your testimony, is it not?

A. Yes, but my testimony is time independent. I was — he described those experiments, and I said those experiments that he described would be reasonably related. I didn't say — and I made no indication in my response of the timing of the experiments.

Q. All right. Now, in your direct testimony with Mr. Rooklidge, you were asked many questions relating to IND applications. Do you recall that?

A. Yes.

Q. All right. Now, do FDA requirements require anything beyond safety and toxicity data in the IND application?

A. Well, I'm not sure what you mean by "require." But I'll answer it this way — the FDA uses everything that's in the IND [2304] to judge the appropriateness of the drug for clinical trials. And, in my experience, they expect to see as much data as is available from the preclinical experiments.

Q. Okay. Do you recall you were also deposed in 1999?

A. Yes.

Q. All right. And you were deposed on two days in that year?

A. That's right.

Q. All right. I'm going to read from your transcript of April 21, 1999. This is page 101, line 14. What other information is needed by the FDA at the IND submission stage other than toxicity and safety data? The IND application.

Answer. The IND application, there are no requirements that it contain anything beyond safety and toxicity.

Now, after giving that answer, you filed what's called an errata sheet; is that right?

A. That's right.

Q. And can you explain for the jury what an errata sheet is?

A. Once I had the chance to review the printed record of the testimony, there were a number of places that I clarified what I had said originally. After reading it, I decided it wasn't as complete or as clear as it should have been, so I made some additions.

Q. All right. Do you see this correction here where it refers to page 101? Do you see that?

[2305] A. Yes.

Q. Okay. Now, did you confer with counsel before making this correction to your deposition?

A. Yes, we discussed it.

Q. All right. And what did you discuss?

A. I discussed with counsel that my answer was incomplete and that I would like to expand upon it.

Q. Okay. And it references here other information that must accompany it, and that it is the IND filing; is that right?

A. That's right.

Q. Okay. And then you go on to state, the Investigator's Brochure and protocol I mentioned earlier and other information. Is that right?

A. That's right.

Q. Okay. Do you still have a copy of Defendant's Exhibit WP?

A. WP?

Q. Yes.

A. Yes.

Q. Okay. Can you show the jury where in Defendants' Exhibit WP it says that an IND filing must show the effectiveness or efficacy of the drug other than — I'll point out one section where it says effectiveness — subpart 5, Investigator's Brochure, and then sub iv, so sub 4. There is a mention there about a summary of information relating to effectiveness in [2306] humans obtained from prior clinical studies. Do you see that?

A. Yes.

Q. All right. Can you point to any other language in this regulation where the efficacy of the drug is required to be submitted with the IND?

A. Well, as we saw on the graphic when we went through the IND application form, there are multiple other areas that the FDA expects to see in an IND application that involve efficacy, and that includes Investigator's Brochure and the protocol. As I've said before, the regulations are rather vague and don't give detailed information to sponsors as to what the FDA expects. These are fairly general.

Q. Well, everything listed here in Defendants' Exhibit WP, with that one exception I pointed out about effectiveness in humans, everything else relates to safety; isn't that right?

A. Well, except the contents of the Investigator's Brochure and the protocol and the contents of the introductory statement and general investigational plan. Those have got to contain evidence — information — about efficacy, because they expect you to explain why you're doing the study, why you're doing it in the indication or the disease that you're studying. And that is part of the background that they expect to see so they just know why you're filing a drug and what divisions should review it.

Q. Okay. Do you see subsection 6 of this exhibit entitled [2307] "protocols"? Starting with the third sentence, "Phase I protocol should be directed primarily at providing an outline of the investigation, an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose or method to be used in determining dose and should specify in

detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries."

Do you see that?

A. Yes.

Q. Now, can you point to any language here that requires the drug sponsor to submit efficacy data in connection with the clinical protocol?

A. As I say, these — these regulations are fairly general and nonspecific and don't give the kinds of information that everybody who has ever done a study realizes is necessary for a protocol. And that is, if you submit a protocol to an IRB, that is the Review Board at the institution, and you don't have any information in there about whether or not the drug works, they are not going to allow that protocol to go forward. They are not going to allow that drug to be given to patients in their institution.

So, for a practical matter, when you submit a protocol, there is no way that your clinical program will work if you [2308] don't have information about the drug and what effect it's expected to have.

Q. I believe you testified these regulations are binding on the drug sponsors; is that right?

A. That's right.

Q. They have to follow these regulations; isn't that right?

A. That's right.

* * * *

APPENDIX 48 — TRIAL TESTIMONY: DIRECT EXAMINATION OF GERD-ALBRECHT LUCKENBACH, PH.D., CALLED BY DEFENDANTS ON MARCH 3, 2000

[Commencing at page 2372]

Q. Dr. Luckenbach, are you familiar with something at Merck called the MEDIS system?

A. Yes.

Q. What is the MEDIS system?

A. The MEDIS system is a data storage system where or which helps to provide documents for submission to regulatory authorities like the FDA.

Q. And while you were the head of Immunopharmacology, were people under your supervision responsible for maintaining the MEDIS system?

A. Yes.

Q. Were you one of the people responsible for approving data that was put into the system?

A. Yes.

Q. What sort of data gets included in the MEDIS system?

A. Well, in the MEDIS system, all data describing the compound are included. These are chemical data, these are [2373] biological data from experiments are included.

Q. And when you directed the data, the input, into the MEDIS system, what was your expectation for how that data would be used?

A. Well, those data would be prepared for submission to regulatory authorities.

Q. From your point of view, working inside Merck in the 1990s, did you become familiar with the steps involved in getting a chemical or compound from when it was first investigated all the way through up to the point where it was ready to be submitted to regulatory authorities?

A. Yes, of course.

Q. What were the steps involved in that process in Merck at that time?

A. Well, we first had what they call a concept group. So this was evaluating an area for interests, innovation, like an indication we were — might add to our current platforms.

Q. Now, when you say —

A. So it was a concept group —

Q. Excuse me. Let me interrupt. You say "indication." What is indication?

A. Well, indication, for instance, would be, in heart disease, you concentrate not generally on cardiovascular systems, you pick out a certain area like congestive heart failure or high blood pressure or something like that.

[2374] Q. And the concept group was responsible for discussions at that higher level of generality?

A. Well, the concept group was on the higher level, but it, of course, went very much into details in evaluation.

Q. What would happen after the concept group decided to focus on an indication?

A. The concept group would forward and present a summary of the work, and this summary would be, well, discussed, evaluated again by the managers, the research managers. And if they approved that concept, then what we call topic group or theme group would be formed, and then practical work would be started.

Q. Did you say topic group or theme group?

A. Yes.

Q. And what was the work of the topic group or the theme group?

A. Well, the topic or theme group, this was consisting of biologists, chemists, and they would put together the appropriate test systems for the biological testings. They would care for the chemistry, synthesis of the chemicals. And that then would start work in that topic group.

Q. And what would happen if the topic group work proceeded to a successful conclusion?

A. Well, if the topic group was successful and was able to define a lead compound, there, again, went through approval, [2375] and then this EPG, developmental group, was formed and decided on.

Q. And at that point the EPG would take responsibility for the lead compound?

A. From that, EPG would take responsibility.

Q. And was that — is that the beginning of the next step in the process?

A. Well, that would be, then, the next step. The EPG has its own budget, has members from regulatory services, from toxicology, from much more developed — well, departments involved in the development of the drug.

Q. I'm going to ask a demonstrative exhibit be placed on the screen here. Sir, would you take a look at this exhibit when it comes up and tell me if you have seen this chart before?

A. Yes.

THE COURT: Can you see it, Mr. Flores?

MR. FLORES: Yes, I can, Your Honor. Thank you.

Q. BY MR. WEIL: Are you familiar with what this chart illustrates?

A. Yes.

Q. Does a portion of this chart correspond with the work you have just been talking about, the work of the theme group?

A. Well, I'd say the first three columns, the columns to the left, the three columns to the left, are characterizing the work of a theme group.

[2376] Q. So the columns to the left of this line here?

A. Right.

Q. Could you describe briefly what each of the columns, what sorts of activities each of those columns illustrates?

A. Well, the column was to the left is you see at the bottom you see kind of Petri dishes.

Q. I'm sorry. Petri dishes?

A. Petri dishes, which probably resemble as the biological test systems, and you have these M & Ms, and they are the different compounds. And the number of compounds shown here probably is — that we go in the first step, we go through a mass screening, as we call it, so many, many thousands — ten thousands of compounds — are tested in one test system to identify active compounds. And then the number is reduced. We have that in the second column. And from that reduced number, again, the chemists and the biologists try to focus, then, on one, two, three compounds which enters into development.

Q. Now, you said these little flat things here represent Petri dishes?

A. Right.

Q. What does this represent here?

A. That's a syringe and a mouse or rodent, and that's animal experiments.

Q. All right. These second two, last two columns, the forth and fifth column, do they correspond to one of the steps you [2377] were discussing earlier in the development process?

A. Well, the fourth column would then be the EPG, and, of course, column to the right then goes really into the — is what leads to the IND.

Q. Now, for purposes of internal discussions or internal usage, does Merck draw a sharp distinction between research on the one hand and development on the other?

A. Well, I'd say this is — it's a more formal distinction, because, I mean, with the formation of the EPG, another process starts. But, of course, as I said before, you get a budget, you have other departments involved. But, of course, before that, in the preclinical or what I think in the theme group work, a lot of experiments have been done which lead to — well, they lead to justifying that compound to enter in the EPG. It feeds into the pipeline. And, of course, these experiments also are designed to aim for regulatory authority approval.

Q. You mentioned some — a formal distinction, though.

A. Yes.

Q. Does the EPG mark a formal dividing line of some sort in the formal institutional sense for Merck?

A. Yes. In the institutional sense, it's —

Q. It's a bright line. What happens — what is the period of time before the EPG called?

A. Well, that's the theme group time, you know. And, I [2378] mean —

Q. What sorts of activity does Merck, in a formal sense —

A. We call it research, research —

Q. What is the activity —

A. And that would be development. But, I mean, this is a gray zone between development and research in the industry, so — I mean, the industry is performing much more developmental work, because it's more focused on development of compound than we were able to perform basic research.

Q. I got up here and started indicating with the pointer, and you responded before I had a chance to ask my complete question.

A. Sorry.

Q. Let me just make sure the record is clear. Prior to the EPG, that work is referred to, in a word, as what at Merck?

A. That I didn't get.

Q. Could you translate that question for me?

(Translation provided.)

THE WITNESS: Well, theme group work.

Q. BY MR. WEIL: Okay. And after the EPG, what is that work called?

A. Well, that's all EPG work, but, I mean, this, of course, is just who does it. I mean, you would say — you would say — officially you would say it was EPG starts development. And before EPG, it's not development. But, as I said, I think [2379] there is a gray zone between — in that area.

THE COURT: Would this be an appropriate time to interrupt your direct examination?

MR. WEIL: Your Honor, I probably have about ten more minutes. We can interrupt now or we can finish up.

THE COURT: Well, we'll take the morning break, members of the jury. Resume at 11:00.

(Proceedings recessed at 10:45 a.m.)

(In session at 11:00 a.m.)

(Jury present)

THE COURT: Mr. Weil, if you please.

MR. WEIL: Thank you, Your Honor. Ms. Brennan very kindly pointed out during the break, we have raised the image of this exhibit, which, by the way, for the record, is ABQ. And I want to call the witness' attention back to the exhibit, then, just momentarily.

Q. BY MR. WEIL: Dr. Luckenbach, here under columns 1, 2 and 3 is written the word "research."

A. Right.

Q. Does that accurately depict the formal internal usage of the word "research" at Merck? Does it cover that — those activities?

A. Well, in part, for sure, yes.

Q. Well, I'm talking now about the formal internal usage

A. Yes. Formally this is research. After this, EPG [2380] development would start.

Q. So the word "development" here under these last two columns, is that also an accurate representation of the formal usage of the word "development" inside Merck?

A. Yes, I would say so.

Q. Well, as a scientist, though, would you say that development work takes place both before and after the EPG?

A. Well, as a scientist, I would say that — well, development work takes place before and after EPG as well as research work takes also place after EPG. That's a continuous process, but in one area. But so the experiments

done, say, in the middle column, and they all feed into the, well, in the data, which will be forwarded to the regulatory authorities.

Q. Is that information that goes into the MEDIS system?

A. That's what goes into the MEDIS system.

Q. Let's talk for a moment about the work being done at Scripps in developing and testing the cyclic compounds pursuant to the 1995 agreement. I want to focus on the time period from 1995 when the agreement went into effect to the beginning of '98 when you left Immunopharmacology.

A. Yes.

Q. Where would you place that work in terms of the columns on this chart?

A. Well, I would place it on both sides of that EPG sign. So [2381] I would place some part into the column, the fourth column from the left, and also in the middle column. So this was in that, what I said before, gray zone. So some work was done was clearly related to development and other work was still research.

Q. So work done under the 1995 agreement fell into this column —

A. Yes.

Q. — to the left of the EPG and into this column to the right of the EPG?

A. Right.

Q. And Dr. Cheresh contributed to the work that was done in both of those columns?

A. Yes.

* * * *

APPENDIX 49 — TRIAL TESTIMONY: DIRECT EXAMINATION OF ULRIKE GRIMM, PH.D., EMPLOYEE OF MERCK AND PROJECT MANAGER FOR EMD-12 PROJECT, CALLED BY DEFENDANTS ON MARCH 7, 2000

[Commencing at page 2774]

* * *

Q. Are you familiar with something at Merck called the MEDIS system?

A. Yes.

Q. What is the MEDIS system?

A. The MEDIS system is a specific software in which all the documents are stored which are required for regulatory purposes.

Q. Have you participated in meetings of the EPG where the issue of what to include in the MEDIS system has been discussed?

A. Yes.

Q. And what is your role with respect to the data in the MEDIS system?

A. I take a look at this and make sure that all of the documents are included and make sure that they are included on [2775] time. And I also make sure that everything is according to schedule.

Q. Do the documents in the MEDIS system pertain to — I'm sorry. Do the documents in the MEDIS system pertaining to EMD 121974 and EMD 85189 contain data generated prior to the beginning of the EPG?

A. Yes. We have a lot of data that were generated prior to the beginning of the EPG.

Q. And does that include data that was generated by experiments performed at the Scripps Research Institute?

A. Yes.

Q. In what form is the Scripps data incorporated into the MEDIS system?

A. We have reports on pharmacological experiments according to our standards, and we also have publications that have been scanned into it.

Q. Publications authored by researchers at Scripps?

A. Yes.

Q. Have you heard the term "good manufacturing practices"?

A. Yes, I do.

Q. And is that sometimes abbreviated GMP?

A. Yes, that's common.

Q. And what does GMP — what do GMP standards require?

A. In general, it means that the company has to see to it that processes are carried out according to standard procedures [2776] in order to ensure good quality.

Q. Does Merck follow GMP standards whenever it synthesizes or tests new compounds?

A. Not always.

Q. When is it necessary to do so?

A. We work according to GMP when substances are used in toxicological and clinical experiments.

Q. Are you also familiar with the term "good laboratory practices" or GLP?

A. Yes.

Q. When is it necessary for Merck to follow GLP standards?

A. When we conduct toxicological studies.

Q. Do you have data in the MEDIS system from experiments performed using non-GMP compounds?

A. Yes, we have a good many.

Q. And is there data in the MEDIS system from experiments that were conducted under other than GLP standards?

A. Yes. We also have the pharmacological reports that do not have to be carried out according to GLP.

Q. Dr. Grimm, in connection with your work, do you have to have some understanding of what regulatory authorities expect in terms of data submitted in connection with applications for regulatory approval of drugs and compounds?

A. Yes, that is absolutely necessary.

Q. And where do you get your information about what [2777] regulatory authorities expect from sponsors like Merck to get a drug approved?

A. I have a number of different sources. First of all, we read the guidelines and apply them in our day-to-day work. In addition, I and my colleagues also visit seminars, we attend seminars and are trained. There is also a member of the team who is specifically responsible for regulatory affairs. And if we think it's necessary, we can also call on external consultants for additional advice.

Q. Dr. Grimm, you mentioned guidelines. What guidelines are you referring to?

A. First of all, the guidelines for EMEA in Europe and for the FDA in the U.S.

Q. Now, with respect to all of the information you've just mentioned — guidelines, discussions, seminars, speaking to consultants — is it important for you to have that information in order to perform your job properly?

A. It is absolutely — it's essential.

Q. What role do consultants play in connection with your project?

A. If we think that we need special knowledge that we do not have within the team, then we turn to consultants.

Q. Let me ask you to take a look at another document there, Exhibit 75. At the top of the document, the first page of Exhibit 75, is written Quintiles Strategic Regulatory [2778] Division. Do you see that, Dr. Grimm?

A. Yes.

Q. Can you identify for the jury, please, who Quintiles Strategic Regulatory Division is?

A. Quintiles is a Clinical Research Organization, the abbreviation CRO is also used, and it's active worldwide.

Q. And looking at this document, can you identify this document for the jury? And by that I mean specifically this first page of Exhibit 75.

A. Yes.

Q. What is this document?

A. This document is the answer received by Sandra Morseth, who is a consultant for Quintiles, and this was with respect to a question we had asked her concerning the plans for the beginning of Phase II in the United States.

Q. Dr. Grimm, did you indicate this document was received by Ms. Morseth or from Ms. Morseth?

A. This is the reply from Ms. Morseth to myself.

Q. Turning to the second page of Exhibit 75, does the second page of the document have the same date as the first page?

A. No. On the second page the date is the 21st of April and on the first page the date is the 1st of May, 1998.

Q. Are these actually two separate documents as they are kept in your files?

A. Yes.

[2779] Q. What is it that this exhibit, 75, contains on the following pages, the pages starting with 02523 and going forward?

A. In order to explain this, I'd like to explain to you the question that we had.

Q. Go ahead.

A. Okay. In the past we carried out toxicological tests on two animal species for a period of four weeks. And then we planned in the United States to begin with Phase II on patients, the patients to be treated for six months. And the question was, does it suffice to conduct four-week toxicological tests if you want to treat the patients for six months.

The first answer from Ms. Morseth was an excerpt from the Federal Register and publication by co-workers at the FDA giving positive information, confirming that this would suffice.

Q. Now, you mentioned consultants, plural. Have you worked with consultants other than Quintiles?

A. Yes.

Q. Could you identify those, please?

A. A company called AAI and another CRO called ICON.

Q. To your knowledge has anyone at Merck had direct contact with anyone at the FDA on the subject of EMD 121974?

A. Yes. Dr. Kramer from Merck had direct contact with Dr. [2780] Andrews from the FDA.

Q. Who is Dr. — is it K R A M E R?

A. That is correct.

Q. Who is Dr. Kramer?

A. He is the head of the Toxicological Division.

Q. And who is Dr. Andrews?

A. He is a co-worker in the subdivision [CETA] at the FDA, but his exact position I cannot tell you.

Q. He works for the FDA.

A. Yes.

* * * *

APPENDIX 50 — TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS L.L. HOUSTON, PH.D., REGULATORY CONSULTANT HIRED BY IXSYS PHARMACEUTICALS, CALLED BY DEFENDANTS ON MARCH 9, 2000

[Commencing at page 3050]

* * *

Q. Now, what role does an introductory — what role did you believe an introductory statement was required to play when you [3051] were finalizing this IND?

A. Yes, the introductory statement basically describes the rationale for the use of Vitaxin, what Vitaxin does in preclinical studies. It gives information about what it is expected to do in these human patients. It also describes some of the toxicities that might be associated with this. This tells you about the mechanism of action of this drug and why it might benefit patients.

Q. Now, turning to the next page, the second page of the introductory statement, and at the bottom lower right-hand corner there is a 3 there.

A. Yes.

Q. Are you with me, sir?

A. Yes.

Q. The first full paragraph begins with the words "preclinical in vitro and in vivo studies to date have shown" — and then goes on to describe something about Vitaxin and what the studies have shown. Do you see that, sir?

A. Yes, I see that.

Q. Did the IND application that you sent in for IXSYS, did that go on to discuss both in vitro and in vivo studies?

A. Yes. There was a considerable amount of information that supported these in vitro and in vivo studies.

Q. Let me ask you to turn next to the Investigator's Brochure. Let me not characterize it. Why don't you turn to [3052] page 12 of the IND submission. There is a 12 in the lower right-hand corner.

A. Yes.

Q. Is this the first page of the new section of the document?

A. Yes. This is the Investigator's Brochure. It's entitled Vitaxin, which is a humanized LM609 monoclonal antibody.

Q. Just for the jury to get an understanding, I'm going to hand you documents that are pages 11 through page 47, so you don't have to pull it out of that binder. Is that the complete Investigator's Brochure that you submitted with the IXSYS IND, sir?

A. Yes.

Q. Let me ask you to turn two pages, page 14, of the submission. What information is contained on this page of the Investigator's Brochure?

A. Yes, this is the table of contents of the Investigator's Brochure. There are various sections in it which deal with important topics of the Investigator's Brochure.

Q. Let me start by asking you to focus on this first section here, the synopsis.

A. Yes.

Q. What sorts of information did you include in the synopsis of the IXSYS IND Investigator's Brochure?

A. The synopsis, again, refers to the rationale of why this [3053] drug might work. It refers to the studies of Dr. Cheresh in the chick CAM model and to other in vitro and in vivo studies.

Q. Let me stop you for a moment. Since you're talking about the synopsis, let me jump ahead to the next page. We can show this as well. You just mentioned that the synopsis discusses a certain model. What was that model, sir?

A. This is the CAM model. I'd rather not try to pronounce chorioallantoic membrane because I always have a problem with it.

Q. Later on in that paragraph does it also mention other work done by Scripps scientists that was included in the Investigator's Brochure?

A. Yes. There is reference to the work of Dr. Friedlander, which describes the rabbit corneal pouch model. Again, evidence which is going to the heart of the mechanism by which Vitaxin might work.

Q. And further on, sir, more references to Scripps work?

A. Yes. There is the reference again to LM609, the parent antibody of Vitaxin to CAM and the SCID mouse/human

skin models. And this is important, again, to show that this molecule has biological activity in an animal model. And it further supports the use of this molecule in human patients as an inhibitor of angiogenesis.

Q. And then, finally, in the next paragraph, it says, "the sponsor has performed additional preclinical models to [3054] establish its, and I believe it is referring to Vitaxin, biological activity which are summarized in this brochure under Preclinical Pharmacology." Was that a true statement, sir, at the time you submitted this IND?

A. Yes. The first paragraph refers mostly to LM609, which was the parent antibody. So all of this data, then, was repeated with Vitaxin, the human antibody, to make sure that it had the same biological and physical characteristics.

Q. And additional information was provided on — what does it go on to say there, sir?

A. Chemistry and formulation, preclinical toxicology and pharmacokinetics, the risk benefit assessment, and some clinical assays.

Q. Very good. Let me turn back, then, to the table of contents. The synopsis in the IXSYS IND was followed by an introduction, other section —

Actually what I want to do is jump straight down to preclinical pharmacology. Could you turn, sir, in the IND to page 18, which is also Bates labeled IX 0048.

A. Yes, I have it.

Q. What, in general terms, were you describing in the preclinical pharmacology section of this Investigator's Brochure?

A. These have two sections. One, the in vitro test tube models, and then data, again, on the in vivo applications of [3055] Vitaxin.

Q. Let me ask you to focus on the in vitro studies. Three are discussed in some specificity. Do you see that, sir?

A. Yes.

Q. What is the first one there discussed?

A. The first one is the characterization of the antibody specificity and its reaction with its potential target.

Q. And that was an in vitro study?

A. This is an in vitro study.

Q. What was the second — well, actually, do you know if that study was conducted under GLP conditions?

A. No, it is not conducted under GLP.

Q. What's the second category of in vitro studies discussed here?

A. The mechanism of action supports the idea that Vitaxin might — should have an effect on cell adhesion. And this was to verify that, in fact, it did have this effect on cell adhesion.

Q. And the title of this section on page B — on page 18, section B, is what?

A. Inhibition of Cell Adhesion.

Q. That was the name of the assay performed?

A. That was the assay.

Q. Was that assay a GLP assay?

A. No, no.

[3056] Q. Let me ask you to turn the page, then, and look at the third and final in vitro study discussed with specificity here in the preclinical pharmacology section of the IXSYS Investigator's Brochure.

What was the title of that third assay?

A. Inhibition of Endothelial Cell Migration.

Q. And was that also a non-GLP study?

A. That is a non-GLP study.

Q. And data from that study was submitted to the FDA in connection with the IXSYS IND?

A. Yes. And, again, it goes to the basic mechanism by which Vitaxin might work and how it might help patients.

Q. Let me ask you to look at page 24 of the Investigator's Brochure. This is a separate section entitled Preclinical Toxicology. Is that correct, sir?

A. That's correct.

Q. And on the first page does it discuss two additional studies performed using the test compounds?

A. Yes. These are two studies of toxicity studies and cynomolgus monkeys.

Q. Now, those toxicity studies, were they performed under GLP conditions?

A. Yes, these are studies that are performed under GLP conditions.

* * *

[3059] Q. Now, do you recall actually filing this IND with the FDA?

A. Oh, very much so. It was a banner day for us.

Q. When was it filed, sir?

A. It was filed on December 30th, 1996, one day before the deadline.

Q. Did you continue to consult with IXSYS after you had sent that document off to the FDA?

A. Yes. It was my responsibilities to follow up on any questions or concerns that the FDA might have. And I was charged with actually shepherding the first six months of the Phase I clinical trial to make sure the patients were treated on time, that all the data was being gathered and handled in an appropriate way, and if there were any problems, I was the point person to solve those problems.

Q. Let me put a demonstrative exhibit up on the screen in front of you. I want to list up here on the screen some of the types of data we've talked about. If we can do that — sir, is [3060] it correct that the IXSYS IND, the Investigator's Brochure, the IND submission, contained data from chick CAM experiments?

A. Yes, it did.

Q. And did it also contain data from in vitro experiments?

A. Yes, it did.

Q. And rabbit cornea experiments?

A. Yes.

Q. And SCID mouse/human skin experiments?

A. Yes. And all of these go to the heart of the mechanism by which it works.

Q. And it also contained data for non-GLP experiments?

A. Absolutely.

Q. So this demonstrative exhibit actually reflects a character of the portion of the data that went in with your IND submission; is that correct?

A. Yes, a very important proportion of that.

Q. Now, in the process of the back and forth with the FDA, after the submission of the IND, did the FDA ever object to the chick CAM experiments?

MR. BECKWITH: Objection, Your Honor, calls for hearsay.

MR. WEIL: I'll rephrase the question, Your Honor.

Q. BY MR. WEIL: Did you ever have any reason to believe that you had made a mistake by including the chick CAM experiments?

A. No.

[3061] MR. BECKWITH: Objection, Your Honor, relevance.

THE COURT: I'm going to overrule that objection.

Q. BY MR. WEIL: Let me ask you the same question about each of the other categories here. Did you believe you had made a mistake, did you ever have cause to believe you made a mistake by including the in vitro experiments?

A. No, not at all.

Q. Did you ever think you had made a mistake by including the rabbit cornea experiments?

A. No.

Q. The SCID mouse/human skin experiments?

A. No, sir.

Q. Did you think you had made a mistake by including data from non-GLP experiments?

A. No, of course not.

Q. What happened after you filed the IND on Vitaxin?

MR. BECKWITH: Objection, Your Honor, relevance.

THE COURT: I'm going to overrule that objection. You may have a continuing objection to any of this testimony.

MR. BECKWITH: Thank you, Your Honor.

THE WITNESS: The FDA had one or two very minor issues, which were dealt with on the spot within a day. Those very, very minor issues were resolved. After the normal usual 30-day waiting period, Phase I clinical trial was started, patients were entered, and Phase I clinical trial was [3062] successfully concluded on schedule.

* * *

[3071] * * *

MR. WEIL: Your Honor, we offer him as an expert in the understanding on research scientists concerning the extent to which their research is or is not the subject of patent infringement claims.

THE COURT: I don't believe he's qualified as an expert in that particular field.

MR. WEIL: Let me ask one more question, then, and I think we can finish with that qualification.

If I may, Your Honor?

THE COURT: Yes.

Q. BY MR. WEIL: Sir, you've discussed how many years — I'll have to lay the foundation for the question with a couple of introductory questions. You've discussed your work as a research scientist over the period of how many years?

A. 33 years.

Q. And in those 33 years you've had interaction at how many conferences and symposia and that sort of thing?

A. Well, I don't — it's very difficult to count all these. 33 years, let's call it 30 years, I go to a conference at least [3072] five or ten times a year. Let's call it six times a year. Six times 30 is 180. And I've probably done 200 or more conferences. So I'm — I've been there.

Q. And in the interactions that you described a few moments ago talking — I think you said grousing — about the obstacles that confront people in your line of work, whether it's as a nonprofit or a for-profit, you listed funding issues, I think you talked about logistical issues, laboratory maintenance issues, personnel matters, regulatory issues. Sir, in all of those interactions, over all of those years, and in all of the work you have personally conducted, did anyone ever once raise with you the issue of whether their experimental research might be the subject of patent infringement claims?

MR. BECKWITH: Objection, Your Honor, leading.

THE COURT: Well —

MR. BECKWITH: It's —

THE COURT: The question is compound, convoluted and the like. Put your question directly.

Q. BY MR. WEIL: In all those conversations, did patents ever come up?

A. Patents very rarely came up. It's just — it was something that was never discussed and certainly in the way that it's being presented in this lawsuit. It was just a nonentity.

THE COURT: I'm going to find he's not qualified to [3073] express opinion as to patent issues.

MR. WEIL: Well, Your Honor, based on that finding, we would excuse the witness and thank the Court for its time.

MR. BECKWITH: I get a shot.

MR. WEIL: Correction. We would indicate that we have no further questions for the witness.

THE COURT: Mr. Beckwith.

CROSS-EXAMINATION

Q. BY MR. BECKWITH: Dr. Houston, we have never met before. My name is David Beckwith and I represent the plaintiffs in this case.

A. Hello, Mr. Beckwith.

Q. Good morning. Mr. Weil put in front of you four big binders from the IXSYS IND.

A. Yes.

Q. You didn't bring those to your deposition, did you.

A. No, I did not.

Q. You were asked some questions about your background, and I didn't hear you mention anything about NuVas. Am I pronouncing that right?

A. Yes, NuVas.

Q. What's NuVas?

A. NuVas is a small L.L.C. company in Sorrento Valley.

Q. Do you have an interest in this company?

A. Yes, I do. I'm the founder of that company.

[3074] Q. And you've used RGD peptides in connection with your work with that company, haven't you.

A. I've used one RGD peptide, which actually is not really an RGD peptide. It's actually, if I can amplify on that, it's a — it was actually a protein domain, which contained an RGD sequence, and that RGD sequence was completely irrelevant to any biological activity that we thought that it might have. But because Mr. Flores asked that question, I wanted to be responsive. That sequence, in fact, does have an RGD sequence. It has nothing to do with any of the biological effects that we thought it would have. We used that protein sequence one time about two years ago. It failed.

We have not used it since. We don't intend to use it since. We don't believe it works.

Q. You also testified, I believe, in your deposition that you may or may not use purified alpha-v-beta-3 with your company NuVas. Do you remember that testimony?

A. Yes.

Q. Now, you wouldn't want to have to pay for a license in order to use these products.

A. I don't believe I have to pay for a license to use these products. You know, I don't — I don't think any — any of the universe of scientists that I work with believe that they need to do this. I think this goes to the whole idea of scientists, research scientists and basic discovery scientists, being able [3075] to operate without the fear of being sued for patent infringement.

Q. My question was directed to you as a co-owner or an owner of NuVas. NuVas is a for-profit company, isn't it?

A. Yes.

Q. Now, Vitaxin is different from LM609, correct?

A. Yes.

Q. And LM609 does not recognize mouse alpha-v-beta-3, does it.

A. No, it does not.

Q. So you can't use mouse studies with LM609, right?

MR. WEIL: Objection, Your Honor, form of the question, vague.

MR. BECKWITH: I'll clarify it.

Q. BY MR. BECKWITH: LM609 wouldn't work on mouse alpha-v-beta-3 because it won't recognize it, correct?

A. I think that's the understanding.

MR. BECKWITH: No further questions, Your Honor.

THE COURT: Any on your part?

MR. WEIL: No thank you, Your Honor.

THE COURT: The witness will be excused.

MR. WEIL: Your Honor, I would suggest at this time a brief break, and in about five minutes we'll be ready to put on our next witness.

THE COURT: Very well. Members of the jury, we'll [3076] take a ten-minute break at this time.

(Proceedings recessed at 11:00 a.m.)

(Jury present)

(In session at 11:20 a.m.)

MR. WEIL: The defendants are now prepared to read into the record the deposition testimony of Mr. Armitage. We have asked someone to come and read the answers from the stand.

THE COURT: Very well. And, again, Mr. Beckwith, you have a continuing objection to all this deposition testimony.

MR. BECKWITH: Thank you, Your Honor.

MR. WEIL: Your Honor, this is the testimony, the sworn testimony, of Robert A. Armitage, A R M I T A G E, taken on Thursday, April 15th, 1999 in this matter. And we have asked to read today Ms. Grace Nakawatase, N A K A W A T A S E.

THE COURT: Members of the jury, the witness, Robert A. Armitage, was sworn at the time of the taking of the deposition.

* * * *

APPENDIX 51 — DEPOSITION TESTIMONY OF EXPERT WITNESS ROBERT A. ARMITAGE, SENIOR PATENT AND INTELLECTUAL PROPERTY COUNSEL, CALLED BY DEFENDANTS, TESTIMONY GIVEN ON APRIL 15, 1999 AND READ INTO THE RECORD ON MARCH 9, 2000

[Commencing at page 3091]

* * *

Q. Is it your opinion that the FDA relies on information regarding the drug screening process?

A. Well, when you talk about the drug screening process, there's so many different things you could be talking about.

Q. Well, like what things do you have in mind?

A. Well, for example, there are high through-put screens that may or may not provide any potentially clinically relevant end point, may simply be used to eliminate compounds that have a certain type of biological activity. There may be other screens that are simply routinely run on any potential drug product that's ever made in a company. There are other biological tests that may only be run on a relatively limited number of compounds because of the nature and complexity of the tests. I mean, if the question is, what, in my experience, does the FDA see of that data, typically they see it all and typically the entire pharmacology of the compound interests would be of relevance to the FDA in the drug approval process. For example, if you do a high-volume screen that indicates that the drug is potentially teratogenic, which might be totally unrelated to, say, its hoped-for therapeutic property

of reducing blood pressure, the FDA would certainly have an interest in those screening results, and the use of the screening data would be reasonably related to the drug approval process. If you were developing a medicine for the treatment [3092] of Parkinson's disease, for example, and you had a screening test for compounds that affected blood pressure, and the screening tests indicated a high probability that the compound would increase blood pressure, and, therefore, producing undesired side effect, that would be important. If the screening tests indicated a high potential to reduce blood pressure, and, therefore, subject the patient to hypertension and potential consequences of losing consciousness, that would be relevant. So you have all kinds of, quote, screening, unquote, that goes on in drug development context, all of which can be relevant to the FDA regulatory process in deciding whether it's safe to go forward with human testing.

Q. The screening I would like you to address is the screening whereby a drug company or a research institute is looking for the best candidate to pursue in the drug development process. In your opinion, does the FDA rely on that type of data generated?

A. You're calling that data screening data. I guess, in my experience, I really call it screening data.

MR. WEIL: Excuse me. For the record, it's "I rarely call it screening data." And then proceeding on on page 203, the question:

What would you like to call it?

A. Well, I would call it biological testing in order — or lead optimization testing or whatever appropriate testing you [3093] want to use, which is typically a lower volume testing than what is normally called screening testing, at least in my experience.

Q. On what do you base your opinion that the FDA would rely on data generated in determining the best candidate, if you will, for pursuing in the drug development process? Or maybe that's not part of your opinion.

A. Well, it's a difficult question to answer, because in my experience there isn't some magic test that you perform that, at the end of the test, each compound gets a grade and then you disregard the Cs and the B pluses and you deal only with the As and the A minuses. Typically what one is always doing is looking for a compound that the FDA will find safe and effective. You are looking for a compound that will be providing the public with advantages over existing therapies. You will be doing any number of tests that will be designed to establish why a particular drug substance is really worthy of the FDA approval process. And, at least in my experience, all of this kind of information is highly relevant to the FDA, because the FDA always measures the efficacy of a compound in terms of its safety. And, therefore, if there is that data that makes it highly probable or more probable or even somewhat probable, that one compound will be better than another. It can be highly relevant to the FDA approval process, highly relevant to a decision as to whether or not it's safe even to [3094] go forward with human testing.

Q. So, in your experience, you have submitted data which shows how you arrived at the best candidate, the assays

that led to the identification of the best candidate that you are trying to get through the FDA?

A. In my experience, you're going to be required to submit the data that you developed. And when you say to tell the FDA why you picked this particular candidate, I don't even know what meaning that has in the regulatory context. What you are going to be telling the FDA is why this particular drug meets the requirements for doing human testing. Later you were going to be submitting to the FDA data as to why this product should be approved as a safe and effective drug often being forced to compare it to other drugs on the market as comparative drugs as your base line for safety and efficacy, and you are not going to get a product approved if the relative risks are not outweighed by the relative benefits based on other therapies available. Indeed, I had a client that just had a new drug application not approved largely because of comparative concerns about the safety of the product.

Q. Compared to its own internal data or compared to other products?

A. Compared to other products on the market in terms of its relative safety and relative efficacy. Obviously it was not a very happy occasion. So while there isn't an overt necessity [3095] to tell the FDA, at least as far as I know, why you didn't pick something else, there is a necessity to demonstrate to the FDA which may, in fact, use the same data, why you believe it's appropriate to go forward or continue clinical trials with a particular agent relative to its properties in comparison to the properties of other substances.

Q. I would like you to limit — I would like you to limit it to pre-IND data. Is your opinion — is it your opinion that the FDA relies on pre-IND data that shows why one compound was chosen by the candidate or by the entity as the basis of an IND application? Do you understand what I mean by pre-IND data?

A. Let's see if we can reach a common understanding. It's the data that you generate that is available for use or submission in the IND when it's ultimately filed.

Q. Correct.

A. Then the issue is, I mean, the ultimate issue here, which can be obscured by all these questions, is, if you are in the pre-IND stage, what is objectively reasonable in terms of testing that will ultimately reasonably be related to the FDA approval process. And I believe the answer clearly is pharmacological rationale for going forward, including the rationale that one develops by comparing a compound to — I hate to use the word "controls," but for lack of a better word — a reference substance or material.

So, for example, if you're attempting, as Glaxo was in the [3096] 1970s, to put ranitidine on the market, you may well want to demonstrate in your preclinical testing that, indeed, you have the same basic pharmacology as cimetidine, which then was the market-leading, anti-ulcer drug and, relative to cimetidine, no particular safety issues, or you may not need to do that. But, in any event, it may be reasonable for you to do that in anticipation of the FDA asking you the question, is this drug safe, is this drug appropriate for either initial human use or for further human studies.

Q. So you are assuming that any assays undertaken to demonstrate a compound of interest to pursue with the FDA —

Did I misread that?

Starting the question again.

So you are assuming that any assays undertaken to determine a compound of interest to pursue with the FDA, also gives you other information that would be relevant to the FDA, is that right, other than screening out unwanted compounds?

A. Let me just see if I understand the issue here. Let's suppose you have ten compounds you are testing and you are trying to pick one for FDA regulatory purposes. And, therefore, you do a rat test to determine whether the compound lowers blood pressure. You do a baboon test to determine whether the compound lowers blood pressure. And then you do a dog test to determine whether the compound has toxic side effects, say, liver, kidney, whatever side effects. Because in [3097] this particular class of drugs, for example, you know that issues can arise with respect to toxicology in dog and the correlation between efficacy in various animal species and with human beings. For each of those compounds which is a potential drug candidate, perhaps based on earlier testing of hypertensive properties, all of those test results are reasonably related to the FDA approval process. Even if your purpose or motivation for undertaking those tests was designed to take the best compound on an aggregate basis for all of those properties, and even if your motivation for undertaking those tests may ultimately have been to meet

some foreign regulatory requirement that had nothing to do with U.S. FDA testing that did explicitly require you to explain the rationale for all drugs you considered and why you didn't select some and didn't select, presumably, one or more that you proceeded with on drug development.

Q. You used animal models in your hypothetical. Would your opinion change, if, rather than injecting ten potential compounds into animal models, an entity instead was screening hundreds of potential compounds using in vitro assays?

A. Well, if you just took the hypothetical I gave and substituted in vitro tests, that were not animal tests, that instead of presumably being tests you would run on ten compounds, you would run on one hundred compounds, necessarily get to the identical conclusion because the reasonable [3098] relationship to the FDA process would be identical.

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APPENDIX 52 — TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS GERALD F. MEYER, FORMER FDA EMPLOYEE, CALLED BY PLAINTIFFS IN REBUTTAL ON MARCH 9-10, 2000

[Commencing at page 3161]

* * *

Q. BY MR. FLORES: Mr. Meyer, you have no formal training in the biological sciences, do you?

A. No, sir, I do not.

Q. Could you explain how it is that you were able to carry out your responsibilities as an FDA official dealing intimately with the problems relating to the drug approval process?

A. Well, probably the short answer is homework and a lot of hard work. I, in 1962, I was at the National Institutes of Health, and I went to west Africa to help the government of Ghana and an NIH team develop its first medical school. And we were always shorthanded then. So I helped do some 1,500 autopsies over two years. I learned to do blood chemistry and clinical chemistry and stool specimens, urinalysis, scrub for liver biopsies, and generally do a great range of things of fixed tissue, staining slides. That taught me a fair amount about the practice of medicine and medical technology and helped me in my jobs at NIH and at FDA.

And then at FDA I spent a lot of time with the medical review staff and the pharmacology staff and others asking questions and trying to learn what was involved in the

processes at FDA. I went and made inspections with FDA [3162] officials, went into firms and learned about processes. So that's how I acquired what experience and knowledge I have.

Q. Could you briefly summarize the principal concerns of the FDA in reviewing new applications for new drugs?

A. Yes, sir. The key issue, the key issue in reviewing an application for a new drug is that it is safe and that it works. And there are a series of stages that one goes through that helps the FDA feel comfortable that this product proposed for marketing is, in fact, safe and beneficial for man.

Q. Now, there has been testimony in this case about different phases — Phase I, Phase II, Phase III — and the review process. You're familiar with those, sir?

A. Yes, sir, I am.

Q. Could you explain what Phase I is?

A. Sure. Phase I is the first time a new pharmaceutical goes into man. And what you seek to learn in Phase I is what does man do to the drug, not what does the drug do to man. You usually put that pharmaceutical in normal, healthy volunteers in small amounts to start. And you are looking to see how does man absorb that drug, how does he distribute it, how does he metabolize it, and how does he excrete it. And then it also includes what I would call dose escalation studies. You start with very small doses, and you start increasing doses for very short periods of time and then for a little longer periods of time. What you're trying to do is get a fix on at what point [3163] does that drug begin to show

some kind of perhaps effect and at what point does it begin to cause some kind of adverse reaction or tolerance problem, at what point does it perhaps elevate your blood pressure or elevate your liver enzymes or give you headaches or cause you nausea. And the reason is because you want to study the drug in larger populations of patients in that dosage range. That's very important. Because if you study the too high dosage range and the person has all kinds of problems in taking the drug, he's sick and he doesn't feel good or he's at risk, then you throw the drug away. You don't develop it because you think it's dangerous. Or if you study the drug at too low a dose, then it doesn't have any effect and you throw it away because then it's worthless. So you want to try to do — use those dose escalation studies in Phase I, sometimes called Phase IIA, but more historically called Phase I, in trying to learn as much as you can about the drug before you move to the next phase.

You're also looking for a very key issue that may be the most fundamental. You want to be — the first time you ever give this substance to man, you want to be sure he doesn't go into anaphylactic shock and die. Never exposed man to this product before, so you do it in a very carefully monitored facility that has — the kind of crash carts you see on ER and things where there is fibrillators and epinephrine and the surgical tools to do a tracheotomy or whatever. You want to be [3164] sure that you are well equipped to monitor that. That doesn't happen very often. In fact, I can't tell you of a case where I am aware where it has ever happened, which is probably a great attribute. But it is something you want to be careful for the first time in Phase I you're going into man.

Q. And Phase II, sir?

A. Phase II is where you go — usually you use patients for the first time. And you, again, you start with short-term studies and then you stretch it out a little longer and a little longer. And these studies are usually about 100 patients that take your test substance and about 100 patients who do not take the test substance. They take a control, either another drug or a placebo, but an inert substance that doesn't have any effect at all. Or, in some cases, you may go to a patient population that had the product as a historical control.

What you — and the study is often what they call double blinded. Neither the patient nor the receiver of the product — pardon me — receiving the product — nor the physician administering it know which is the test substance and which is the control. The products are made so they all look alike. They are coded numerically and they are randomly assigned formally using either a computer or numbers to make sure that, when you get through, the results are not influenced because the patient knew this guy got the real drug or this guy [3165] got the control, or to make sure the patient isn't influenced. You really want those results to be free of that.

Q. And typically how many patients are involved in Phase II studies?

A. Well, usually at least two studies of about 200 patients. Sometimes more. But you want to be — you want to be cautious about that. These things cost money. And those monies contribute to, ultimately, the cost of the pharmaceutical. Costs for the — on the average, it costs about $5,000 a patient to do a study. So, you know, two, maximum number of ten, studies of 200 patients.

Q. Now, Phase III, could you describe that briefly?

A. Sure. I need to tell you first, though, that if, in fact, at the end of Phase II you've got at least two studies that show that the product works and no studies that show there is a serious patient problem, in terms of adverse reaction, FDA can probably and will approve the product. Now, most of the time, unfortunately, you don't have that. You have a product that shows it works a little but not in everybody and you have some side effects. So then they ask you to do Phase III studies, which give you up to about 1,500 to 2,000 patients in total.

And what you're looking here is to get enough additional exposure to the drug that statisticians can say, with certain statistical confidence, this works. And to show that the side effects that you have in 2,000 patients or so are not serious. [3166] Not at least so serious they would outweigh the benefit of the drug. That's the final principle again, that the benefits of this drug outweigh any adverse reactions, outweigh any risks to the patient.

Q. Now, the benefits of the drug, the extent to which it works or doesn't work, what kind of data does the FDA use to make its evaluation of that?

A. Clinical data in humans.

Q. Human data.

A. Yes, sir. That's the only thing they base their decision on.

Q. Do they — do they ever base it on — do they ever base the decision of how well the drug works on data on animals?

A. Not — not really. The animal data that is developed is used to substantiate safety before you go into man. And then indirectly you look at the animal data to see if it gives you any signals that you should watch for when you are evaluating this product in man. But you don't approve a product based on animal data, no, sir.

Q. It's human data?

A. Human data, yes, sir.

Q. Now, you talked about Phase I where the proposed drug is first given to humans and circumstances in which that is done with the control facilities and — what did you call those carts, the crash —

[3167] A. Well, the classic term is the crash cart. It is an emergency room set of equipment that is usually mounded on a cart so you can wheel it from one stretcher to another, if necessary.

Q. Now, does there have to be a specific approval by the FDA before a drug, a proposed drug, is given to any human beings in Phase I clinical trials?

A. Yes, sir, there does. It's called an Investigational New Drug Application that is submitted. It's an IND is the short form, yes.

Q. And what is the purpose of the IND?

A. Well, the purpose of the IND application, I assume you mean, is to provide FDA with substantiation of safety based on animal data that permits you to make a — to feel comfortable or secure that you believe you will be safe in going into some normal healthy volunteers in small amounts on a basis of Phase I.

Q. Does the FDA have requirements that it imposes on the animal data that's necessary to establish —

A. Yes, it does. It has a — it requires that the animal data, the animal toxicology data particularly, and prefers that all of the data submitted, be done in accordance to what I refer to as good laboratory practice regulations. And these are regulations that are not really all that burdensome. And I say that from having run a company. And that's what's one of [3168] our businesses was doing that kind of testing. And the fact is that, what it amounts to is some very careful documentation of what you are going to study, what happens, and a fair discipline about keeping good records, signing those records, if there is a change in the records, explaining why there is a change, if there is a deviation from the protocol, recording it. I would say those are the requirements that are consistent with any good scientific experiment. And it is a kind of a discipline that you incorporate into the way in which you do your work. You find the same kind of discipline incorporated in many process manufacturers —

MR. ROOKLIDGE: Objection, Your Honor. This is far beyond the scope of his expert report and deposition testimony and I ask it be stricken.

THE COURT: Yes.

MR. FLORES: Your Honor, Mr. Meyer's expert report directly addresses GLP requirements.

THE COURT: Well, it's a long answer and I think it's gone beyond the question. I'll let the answer stand as it is. Put your next question.

MR. FLORES: Thank you, sir.

Q. BY MR. FLORES: Now, I think you said there are certain kinds of studies on which good compliance of good laboratory practice is required?

A. Yes, sir.

[3169] Q. And what kind of — what were the studies where that's required?

A. The animal toxicology studies that are used to evaluate safety of the compound in animals and substantiates safety to FDA for the purposes of evaluating whether the substance may be used in man.

Q. And did you say that there were certain types of data relating to safety for purposes of the IND for which good laboratory practices is not required by the FDA?

A. Well, the regulations are not as specific as one might like. But the practice is, by FDA, is to seek to have all of the data submitted in safety to be, in fact, performed consistent with good laboratory practice regulations.

Q. Now, you talked about the safety-related studies in connection with the IND that the sponsor has to submit have to be relating to animal data. Is there — will any animal data do or are there certain animals that are required or preferred by the FDA?

A. No. One needs to — one needs to use animal species that will have some predictive value for human experience based on the long history of science in this area, in the toxicology area. Those are primarily mice, rats, hamsters, guinea pigs, and, less frequently now, dogs and monkeys.

Q. Are you familiar with a type of assay called a chick CAM assay?

[3170] A. Yes, sir, I am, somewhat familiar with that, yes.

Q. What's your understanding of the nature of that assay?

A. Well, my understanding of the nature of that assay is that it is a test to assess the ability of a substance to stimulate the growth of blood vessels in a chicken embryo, in an egg, or to test the ability to inhibit the growth of blood vessels in the membrane of that egg.

Q. Is data from a chick CAM assay acceptable to the FDA to bear on safety issues relating to an IND application?

A. I do not believe that data would have any value when substantiating data, in substantiating the safety of a substance in an IND application, sir.

Q. And would you explain the basis for your opinion?

A. Well, I don't believe that chicken data has ever been considered to be predictive of the human experience. And, in addition to that, we actually tried — we actually had some staff who some years ago tried to use that assay as a test for the safety of food additives, and it was just — just didn't work. We just discontinued it. It's considered by — to be a useful discovery screening kind of tool to evaluate the ability to stimulate and inhibit blood vessel growth.

Q. Are you familiar with the type of assay referred to as a cell adhesion assay?

A. Somewhat, sir, yes, sir.

Q. And could you explain your understanding of that type of [3171] assay?

A. Well, that's a — that's a way of treating mouse cells in what's called tissue culture in a dish to see if a substance will help them adhere to a plate coated with protein. I actually don't know what value, particular value, that test has. I don't —

Q. Did you have an opinion as to whether a cell adhesion study such as you described would be acceptable to the FDA, would be relevant to the FDA, in the IND review process?

A. I —

MR. ROOKLIDGE: Objection, Your Honor. This goes beyond the scope of the deposition testimony and the expert report. The deposition testimony and the expert report were directed to what was required for the IND.

THE COURT: Well, I think this question bears on that, and I will allow the answer. Overruled.

THE WITNESS: I don't believe they would have any value, again, in substantiating the safety of a compound to be submitted for the possibility of evaluating it in man.

Q. BY MR. FLORES: Now, you talked about how — at the IND stage, is the FDA concerned with the efficacy of the drug, whether it works, is that balanced against safety considerations?

A. No, sir. At the time of the IND stage, there is no information about efficacy in man. And at this point I don't [3172] know of any situation where possible effectiveness in animals would be predictive of behavior in man.

Q. Do you know of any studies that —

A. Excuse me, sir. I need to qualify that. I am talking about a compound that has not previously been used in man. If you had a drug that was approved for some other purpose in man, then the data associated with that other approval might have some value.

Q. Now, Mr. Meyer, you have attended pre-IND meetings, haven't you? I believe you testified —

A. About two or three a year since I've been a consultant. And probably about one every month or two when I was at FDA, yes, sir.

Q. Is it FDA practice to require that the discussions at those meetings be recorded?

A. Absolutely.

Q. In a written — is that —

A. That is spelled out in the regulations. In part X, one of the subsections very specifically say that, when anything is discussed that may subsequently be referred to, and that's just about anything in the context of an application, there must be a written memorandum.

Q. Did you have an opportunity to review Mr. or Dr. Bynum's testimony in this case?

MR. ROOKLIDGE: Objection, Your Honor. Once again, no.

* * *

[3174] A. Well, the FDA does not automatically accept clinical data from U.S. or European trials. FDA does accept data from studies done in Europe. I have published an article —

THE COURT: He's gone beyond the question.

THE WITNESS: Okay.

THE COURT: Go ahead with your next question.

Q. BY MR. FLORES: Does the FDA — under what circumstances does the FDA accept clinical data from European trials?

THE COURT: You will have a continuing objection, Mr. Rooklidge.

THE WITNESS: Anytime that data is conducted in accordance with U.S. requirements, U.S. FDA requirements, regardless of where it is done, it is acceptable.

Q. BY MR. FLORES: Does it make any difference in terms of acceptability to FDA whether clinical trials are performed in Europe or in the United States?

A. No, sir, not if it meets FDA's requirements.

Q. And do you know whether clinical trials performed in Europe typically meet FDA requirements?

MR. ROOKLIDGE: Objection.

THE COURT: Sustained.

Q. BY MR. FLORES: Is it FDA practice to require applicants submitting an IND to submit data showing that they have searched for the best drug candidate?

A. Would you repeat the question, sir?

[3175] Q. Is it FDA practice to require IND applicants to submit data indicating that they have selected the best drug candidate among a number of different options?

A. No, sir, that's not relevant to FDA's decisions.

Q. Does the FDA generally require submission of data generated for compounds other than the compound that is the subject of the IND?

A. Not in my experience, sir.

Q. Does the FDA — I think you talked about this a bit in an earlier question. Does the FDA have formal programs for educating the community of potential drug sponsors on FDA requirements?

A. We have a number of approaches we use. I've never thought of it as kind of a formal program. We sponsor seminars, we sponsor video seminars that are broadcast all over the country and to Europe. We participate in a number of meetings specifically for that purpose sponsored by the Food and Drug Law Institute, the Drug Information Association, the Pharmaceutical Education and Research Institute where we provide faculty. So we do that, but I'm not sure I'd describe it as a program per se.

Q. Would you describe it as an effort by the FDA?

A. Very substantial efforts.

Q. Now, the practices, the policies, that you described here today about FDA requirements relating to IND submissions, has [3176] the FDA made an effort to make the community of potential drug sponsors aware of these practices and policies?

A. Very substantial. We produce guidelines, we have held seminars, we have met individually, we have incorporated steps in the process that tried to provide as much

help as we can within available resources within that agency. I say that as a former FDA official.

Q. How many companies, if you can approximate, have you provided consulting services relating to drug application process?

A. Probably over a hundred. I don't know that for sure. I mean, I don't have a count per se, but I — that's what I do all day long, seven days a week.

Q. Now, you have in front of you, Mr. Meyer, a copy of your C.V.?

A. Yes, sir, I do.

Q. And that is — there is a trial exhibit sticker there.

A. Yes, sir.

Q. What's the number?

A. 534, sir.

Q. Is that a true and accurate summary of your professional qualifications and experience?

A. Yes, sir.

MR. FLORES: I have no further questions, Your Honor. I would offer Exhibit 534 into evidence.

[3177] THE COURT: We'll take it up.

Mr. Rooklidge, you may begin your examination, if you wish.

MR. ROOKLIDGE: Thank you, Your Honor.

CROSS-EXAMINATION

Q. BY MR. ROOKLIDGE: Good afternoon, Mr. Meyer. My name is Bill Rooklidge. I represent the defendants in this case, and we haven't had the opportunity to meet before.

Let me hand up to you some of the exhibits that we'll be using.

A. Thank you. Pleased to meet you.

Q. Very nice to meet you.

You testified earlier today that your work at the FDA didn't involve approving applications; is that correct?

A. No. If that's the impression I left you with, that's incorrect. I did not sign the approval of an application, but all my work involved the approval of applications, yes.

Q. Well, you didn't hold a scientific review position, did you, at the FDA?

A. No, sir.

Q. Now, your day-to-day job duties at the FDA didn't include working with drug sponsors to review their scientific data, did it?

A. I did not review scientific data, no, sir.

Q. And you didn't design preclinical tests?

[3178] A. No, sir, I did not design preclinical tests.

Q. And you didn't conduct preclinical tests?

A. I certainly did not conduct them. FDA does not do that.

Q. Right. And you don't consult on the scientific details of preclinical tests, do you?

A. I do with the help of usually a specialist in the area, sir.

Q. Right. You have to bring somebody in to handle the scientific details.

A. Yes, sir, that's correct.

Q. Okay. And you don't design or conduct clinical trials.

A. No, sir.

Q. Now, during your deposition you drew a distinction between having scientific input and managerial input. It's fair to say, isn't it, that your input in clinical and preclinical studies has been more managerial input rather than scientific input?

A. Well, I'm not sure I recall describing that, sir. Did you say in my testimony here this afternoon?

Q. Yes. No, in your deposition.

A. Oh, in my deposition.

Q. Do you remember having your deposition taken back in May of 19 —.

A. Yes, I do.

Q. Okay. And did you remember drawing the distinction [3179] between having scientific input and managerial input?

A. No, I don't remember that, sir. I don't — I'd have to see it, I guess.

Q. All right. Well, would it be fair to say that your input in clinical and preclinical studies has been more managerial input rather than scientific input?

A. I would have described it as more strategic rather than managerial, sir.

Q. Now, you're also not a lawyer; is that correct?

A. That's certainly correct. I'm not a lawyer.

Q. So you're not an expert on the FDA Exemption to patent infringement, 35 U.S.C. Section 271(e)(1).

A. Not in any way, sir.

Q. So you're not here to testify about whether any activities are exempt or not exempt for patent infringement.

A. No, sir, I'm not. I mean, yes, sir, I'm not here to testify for that reason.

* * * *

APPENDIX 53 — TRIAL TESTIMONY: DIRECT EXAMINATION OF EXPERT WITNESS GERALD F. MEYER, FORMER FDA EMPLOYEE, CALLED BY PLAINTIFFS IN REBUTTAL ON MARCH 10, 2000

[Commencing at page 3231]

* * *

Q. Now, the FDA requires that this portion of the IND application, the introductory statement and general investigational plan, includes a description of the rationale for the drug or the research study, doesn't it?

A. Yes, sir, I believe it says that.

Q. And in order to know what the rationale for the drug or the research study is, the drug sponsor has to perform some experiments that's going to give it an idea of what that rationale is, isn't that right?

[3232] A. Usually, yes, sir.

* * *

[3236] * * *

Q. Now, in the regulation it spells out what the FDA is looking for in pharmacology and toxicology information, and it says, adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro.

So let's stop there for a second. The FDA understands that or says here that it will accept data either for studies in animals or in vitro, is that right?

A. Yes, sir, that's correct.

Q. And it also says it wants adequate information. Does the regulation go on anywhere to define what is adequate?

A. I don't believe so, without reading it again at the moment.

Q. Well, in fact, doesn't the drug sponsor have to use its discretion to identify what is adequate information?

A. That's correct. But — and you must keep in mind that here it is, the information that he has used, as a basis to [3237] conclude that it will be safe to go into humans. That is the basis of providing that information, sir.

Q. And it's information both on pharmacology and toxicology; is that right?

A. Yes, sir, that's correct.

Q. Let's, then, go to 23(a)(8)(i), which is this section down here. Now, this section identifies that the FDA wants to see evidence on pharmacology and drug disposition. In fact, it says a section describing the pharmacological effects and mechanisms of action of the drug in animals.

What is the mechanism of action?

A. Well, that is how does the drug work, if known. That isn't always known in some new products that are being

developed and some new chemical or molecular entities. But if it is known, do you know how it actually works, what does it do inside the body to achieve its effect.

Q. I'm sorry. You said how it works and what does it do?

A. Or what does it do inside the body to achieve its effect.

Q. And, once again, the drug sponsor needs to exercise its discretion in what evidence it's going to submit on mechanism of action, isn't that correct?

A. Yes, sir, on anything.

Q. So the drug sponsor, then, has to exercise its discretion submitting information about how the drug works and what does it do; is that right?

[3238] A. Yes. Assuming, again, under the general rubric of substantiating that it will be safe to use in humans.

* * *

[3242] * * *

Q. BY MR. ROOKLIDGE: Okay. Let's turn our attention to the GLP requirements that you've discussed. Now, the Federal Regulations set out what information is subject to the GLP requirements and what those requirements are, don't they?

A. Well, not nearly as precisely as what is, in fact, in their practice, that's correct.

Q. Okay. Now, you testified yesterday that not all of the scientific information that's submitted to the FDA in an IND application needs to be GLP data, isn't that right?

A. Well, I think if you read the regulations, you find that it refers — and the guidelines — it refers to toxicology data, and then one has to wonder about pharmacology data.

Q. Right. So the regs. only explicitly require that the toxicology data is required to be GLP.

A. As currently worded. But if you speak with the review staff at FDA, they will tell you —

Q. I'm just asking about the regs. at this point. We can go into what the regs. and the guidances say, but let's take a look first at those GLP requirements themselves from the regs.

If you could turn to Defendant's Exhibit ABZ. Have you ever seen this document before?

[3243] A. Yes, sir, I have.

Q. Okay. Now, Exhibit ABZ is part 58 of the Code of Federal Regulations that applies to the FDA, isn't it?

A. Yes, sir.

Q. And you've relied on these particular regulations in your work, both at the FDA and in your consulting practice?

A. Yes, sir.

Q. Now, if we look at the beginning of this provision, it explains that this part prescribes good laboratory practice

for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration.

Do you see that?

A. Yes, sir, I do.

Q. Okay. Now, nonclinical laboratory studies has a special definition, doesn't it?

A. Yes, sir, it does.

Q. Okay. Now, later on in that same section it goes on to say that compliance with this part is intended to assure the quality and integrity of the safety data. Is that correct?

A. That's correct, sir.

Q. Okay. Now, if we go down a little further in that section, it actually defines what nonclinical laboratory study means, doesn't it?

[3244] A. Yes, sir, it does.

Q. Okay. And this definition means that nonclinical laboratory studies — doesn't mean everything, but it's much more specific than that, doesn't it?

A. Well, it attempts to explain that, yes, sir, it does. And it tries to exclude basic exploratory studies from those studies that are — in which test articles are studied prospectively.

Q. And it also, in this and in the guidances that interpret it, makes it very clear that what this is directed to is studies that are conducted to show safety. Isn't that right?

A. Yes, sir, that's correct.

Q. Now, you explained yesterday that the FDA recommends that all of the data that's submitted to it be GLP data, didn't you?

A. Nonclinical data, yes.

Q. Nonclinical data, correct.

A. The clinical data is subject to good clinical practice regulations.

Q. In effect, then, the sponsor needs to exercise its discretion about how much of the data, the non-safety data, that it submits to the FDA, is going to be GLP data, doesn't it?

A. Well, it could exercise its discretion about how much of the non-safety, nonclinical data it submits generally.

Q. Right. Now, let's go back to the safety data. If the [3245] sponsor submits safety data that is GLP, can it submit additional data that might inferentially bear on safety that is non-GLP?

A. Well, there is nothing in the regulations anywhere that says a sponsor cannot submit anything. In other words, a sponsor can submit incredible amounts of things that may have little to do with the decision that FDA makes, if the sponsor is so inclined.

Q. Right. And the sponsor has to exercise its discretion in that regard, doesn't it?

A. Well, it's certainly proven to do so, for two reasons. First of all, if they submit enormous amounts of things, it only protracts the review. And the second thing is, if you talk — if we were to bring Dr. Robert Temple here, who is the most senior reviewer at the moment at the FDA, and if you were to ask him, is there merit in submitting a lot more than is necessary, he would say no, because it suggests that you are trying to bury something or hide something.

Q. Right. And for that reason —

A. So it alerts him to — or it makes him nervous, rather, that there is something in that data that is sort of buried that he's really got to search for.

Q. Right. And for that reason, then, the sponsor has got to exercise its discretion in balancing the kinds of data that are absolutely required and the kinds of data that the sponsor [3246] thinks is going to be helpful to the FDA, isn't that right?

A. Yes, sir.

Q. Okay. So the sponsor has to exercise discretion in things like GLP data, in vitro and in vivo data, mechanism of action, pharmacology, how the drug works, what the drug does —

A. Well —

Q. — and all those kinds of things, doesn't it?

A. Yes, sir. But he is supposed to submit all data which he believes will bear on the safety of the product.

Q. Right. And to the extent that the sponsor wants to include additional data, the sponsor has to exercise its discretion.

A. It's free to do so, sir.

THE COURT: Mr. Rooklidge, are you requiring additional time?

MR. ROOKLIDGE: No, Your Honor. The only time I require at this point is to move into evidence the FDA regulations of ACA and ABZ.

MR. FLORES: No objection.

THE COURT: Mark in those exhibits.

MR. ROOKLIDGE: Thank you, Mr. Meyer.

THE COURT: We'll take our morning break at this time, members of the jury, for 15 minutes.

THE WITNESS: Does that mean I'm excused again?

THE COURT: No. You have to come back to answer [3247] questions for the other side.

THE WITNESS: Okay. Thank you, sir.

(Proceedings recessed at 10:30 a.m.)

(In session at 10:45 a.m.)

(Jury present)

THE COURT: Mr. Flores.

MR. FLORES: Thank you, Your Honor.

REDIRECT EXAMINATION

Q. BY MR. FLORES: Mr. Meyer, you had a deposition there in front of you in the regulations on nonclinical studies? I think it's on the second page of Defendant's Exhibit ABZ.

A. Yes, sir.

Q. And this regulation, in part, sets out, part of it talks about what is not a nonclinical study, and I think you referred to that in your testimony here this morning. Do you see that, sir?

A. Yes, sir, I do.

Q. And what is the portion of the regulation there that says what is not a nonclinical study?

A. It is the third sentence, sir, in that definition. And it makes clear, it says, and quote, the term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test substance, test article.

Q. Now, Mr. Rooklidge also asked you a couple of questions [3248] about this portion here, the requirements relating to toxicology and pharmacology information. Do you recall that?

A. Yes, sir, he did. They were, I believe, under the content and format of an IND, 312.23, sir.

Q. And I think you testified about how drug sponsors have to use their judgment regarding the information that pharmacology and toxicology information that should be submitted? Do you recall that?

A. Yes, sir, I do.

Q. Does this regulation give a basis for the exercise of that judgment?

A. Yes, sir. It makes clear that the information that they want is the information on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. What is the information that the sponsor used to substantiate, in his judgment, that this product can safely be given to humans.

MR. FLORES: Those are all the questions I have.

MR. ROOKLIDGE: Just a few brief follow-ups, Your Honor.

RECROSS-EXAMINATION

Q. BY MR. ROOKLIDGE: Mr. Meyer, you've just explained that the regulation that defines nonclinical laboratory excludes from the definition of nonclinical laboratory study basic exploratory studies carried out to determine whether a test [3249] article has any potential utility or to determine physical or chemical characteristics of a test article. Is that right?

A. Yes, sir.

Q. So this section here says those kinds of tests don't fall within the definition of nonclinical laboratory study, isn't that correct?

A. Yes, sir, that's correct.

Q. Now, the FDA has also provided some guidances on other areas that the term nonclinical laboratory study excludes, hasn't it?

A. I'm not sure what you're referring to, sir.

Q. Well, why don't we turn to Defendant's Exhibit CP, which should be in front of you.

A. What is that, sir?

Q. It's Center for Drug Evaluation and Research Guidance for Industry.

A. All right.

Q. Now, the Center for Drug Evaluation and Research, you worked there, didn't you?

A. Yes, sir, I did. I was their Deputy Director.

Q. Correct. And so what is this document that's Defendant's Exhibit CP?

A. It is a guideline. This is a guideline that was published and issued, it says prior to February of 1997, FDA — I don't remember, but I'm concluding, must conclude, that the FDA [3250] published a revised guidance practices in February 1997.

Q. Let's take a look at, I think it is five pages in or so of this document, there is a question about the definition of nonclinical laboratory study. Do you see that?

A. Yes, sir, I do.

Q. Okay. And it says that the definition of nonclinical laboratory study excludes field trials in animals. And then it goes on to ask, what is a field trial in animals? Do you see that?

A. Yes, sir, I do.

Q. Okay. And the answer explains that a field trial in animals is similar to a human clinical trial. It is conducted for the purpose of obtaining data on animal drug efficacy and it is excluded from coverage under the GLPs. Is that right?

A. Well, it says that, yes, sir.

Q. Okay. So the bottom line from this is, if you are conducting studies on animals for the purpose of obtaining data on efficacy, isn't that excluded from the GLPs?

A. That's what that guidance says, yes, sir.

Q. Well, let's then go to document AAP, Exhibit AAP. You should have that in front of you.

A. Good Laboratory Practice Regulations.

Q. That's correct. Do you recognize what that document is?

A. Yes, sir, I do recognize the document.

Q. What is that document?

[3251] A. I'm sorry. I know what good laboratory practice regulations are. I'm not sure I've seen this one before. This says that it is the, a post-conference report on some management briefings that were made in 1979.

Q. And is this a publication of the FDA?

A. Well, yes, but there are later publications, sir, that — than this.

Q. The later publications that address this same subject matter?

A. Certainly that address good laboratory practice regulations. Frankly, the good laboratory practice regulations were edited well after — were revised well after August '79. This says minor editorial and formatting changes were made in '98, so that makes it current.

Q. Okay. Why don't we turn — I've tabbed one of the pages for you there, and there is a question and answer that provides some additional guidance to industry. And the question is, does the term "nonclinical laboratory study" include animal laboratory studies, which are designed for the explicit purpose of determining whether a test article has reasonable promise of clinical effectiveness, and in which observations bearing on clinical safety are only incidental or fragmentary or, at most, clearly secondary? Do you see that?

A. Yes, sir, I do.

Q. Okay. It goes on to answer, no. Is that right?

[3252] A. That's what it says, that's correct.

Q. Okay. So if a sponsor is conducting tests for some purpose of, other than safety, in fact, for effectiveness, but that also gives the sponsor some idea about safety, that's not covered by the GLP regs., is it?

A. It says it is not here, that's correct.

Q. Okay. And so that if a sponsor is conducting a study, for example, on animals, and when it provides that drug to animals, the animal doesn't die, that would incidentally or fragmentarily provide some information on safety, wouldn't it?

A. Well, I think if anything untoward happened to the animals that were involved in that study, including short of death but that were serious, you'd have to consider that also as safety data and submit it on that basis, too.

Q. Okay. Because it would incidentally bear on that, even if the purpose of it was to show effectiveness.

A. In that case, yes, sir.

Q. Okay.

MR. ROOKLIDGE: Your Honor, at this point defendants would move into evidence Defendant's Exhibit AAP and Defendant's Exhibit CP.

* * * *

APPENDIX 54 — BENCH HEARING RE DEFENDANT'S OBJECTIONS TO PLAINTIFFS' PROPOSED JURY VERDICT FORM, HELD ON MARCH 16, 2000

[Commencing at page 3684]

* * *

MR. WEIL: I want to focus very briefly and make a record on one particular dispute that came up over the form [3685] that's been adopted.

The Court elected to choose for the question regarding the FDA Exemption an all-or-nothing approach.

THE COURT: Right.

MR. WEIL: That is, if the jurors are to find that all of the activities are exempt under the FDA Exemption, then they do not answer the question about damages, there are no damages, and the verdict form is completed, signed and submitted.

Under the present form — under the form as it has been settled upon, if they find that any single event, any single experiment or activity, is nonexempt, then they proceed to the damages analysis.

The defendants' concern with that, the way the analysis is now framed, is that it is not clear whether the jury is to analyze damages without regard to exemptions that may apply or to analyze and provide damages based only on those activities which are nonexempt. And for that reason we had

asked that the Court instruct the jury on the damages question inserting the clause, setting aside, for this question, the issue of the FDA Exemption. Because it seemed to me in our discussions and it seemed to be clear from the position taken by Ms. Brennan that it was the intention of the Court to instruct the jury that, if any activity was found to be nonexempt, then all of the exemptions should be disregarded for the purposes of the damages analysis.

[3686] I offer for the record one piece of evidence that suggests that the defendants have not themselves embraced this all-or-nothing approach. I flipped quickly to yesterday's closing argument and noted on page 3549 that — and also in the pages prior to that — that Ms. Thayer, in addressing the issue of the exemption, clearly pointed out that the witnesses had come and discussed on an activity-by-activity basis why certain activities were exempt, and that, while there had been a response as to some of those activities on the part of the plaintiffs, certain others have been completely disregarded. And Ms. Thayer, I think, argued persuasively that, as to those activities at least, a lack of — the application of the exemption should be a foregone conclusion.

If the jury finds that certain activities are exempt and others are not, based on the current verdict form, it is going to be adrift. It will not know, for example, if it determines that the only nonexempt activities are activities that were not part of a drug development process. If the jury reasons developing drugs is exempt, if the application is now in for this drug, we're going to find for those activities are exempt, but they have concerns about other activities, for example, the activities of Dr. Storgard, which didn't contribute

relatively directly to the submission of this particular compound, arguably, if they reach that conclusion, decide that the only nonexempt activities are activities that did not in their view [3687] lead directly to a drug development project, they are going to be in a quandary. Do they apply the exemption and base damages based only on nonexempt activities? Which would lead to no damages at all. Or do they ignore the exemption and consider the entire body of accused — of accused experiments as the basis for a damages award.

So, again, thank you, Your Honor, for allowing us to make this record. We will — we may submit one brief argument on this particular point as well. And I certainly hope that Ms. Brennan will respond if I have in any way mischaracterized their —

THE COURT: No, I'm going to indicate this matter was fully argued, extensively argued informally, and I had rejected the proposal by the defense on the grounds that the — at the time of the final summations and based on the underlying evidence, that there wasn't a sufficient basis to identify particular activities or experiments or research that might have fallen outside of the exemption or from others that might have — that may well have been included within the exemption, that this would cause more difficulty and confusion on the part of the jury, that I would find that there wasn't enough support in either the underlying evidence or in final summations upon which the jury could make an adequate and competent decision. So that's why I rejected it.

* * * *

APPENDIX 55 — EXCERPT FROM DEPOSITION TESTIMONY OF LOTHAR H. FINKE, M.D., DIRECTOR OF ONCOLOGICAL CLINICAL DEVELOPMENT AT MERCK, GIVEN JULY 23 1997, PLAYED AT TRIAL ON FEBRUARY 14, 2000

[Commencing at page 1]

Q. Would you state your full name for the record, sir.

A. My name is Dr. Lothar Herbert Finke.

A. You were asking for my professional and scientific background and career, not my entire CV, correct?

BY MR. FLORES:

Q. Let me explain a little. You don't -- would not ask Dr. Finke to list his publications or to list every minor or major award or credit he may have. What I'd like is an overview of his education and the principal positions he has held both academically -- in academia and industry.

A. After having finished secondary school with the university entrance examination, I started studying medicine, human medicine at Marburg in 1984, and after the fourth semester there I also took up cell biology.

During my activity or during my time -- strike activity, please -- at the Max Delbrueck Center, was a guest scientist at the Basel Institute for Immunology.

Now, in that situation where according to the German further -- German educational and training system, I would

have had to make a decision whether I would become a specialist in sur[illegible]y, which was not my primary interest, or continue in basic research, I looked for a new job and decided to take up the position at Merck, which made use of all my previous experience and knowledge acquired and was meaningful to me, on the 13th of November, 1995, where I took up when I took up the position at Merck.

At Merck I'm in charge of the clinical development of oncological and immunological development projects.

This also comprises responsibility for taking projects from the clinical to the -- I'm sorry -- from the pre-clinical to the clinical phase.

I think this should have characterized my CV up to that time.

* * *

[4] Q. Is this a copy of a memorandum which you drafted?

A. Yes, it is.

Q. Do you recall -- As you sit here today, do you have a present recollection of drafting the document?

A. Yes.

Q. And do you have a present recollection of being presented with a letter from the Legal Department on the Friday of the week prior to this letter?

A. I cannot remember the situation at all.

Q. Would you translate the document, that is read it in English for the record?

THE INTERPRETER: The whole document?

MR. FLORES.: Yes.

THE INTERPRETER: To Erhard Schnurr, S-C-H-N-U-R-R, Merck. Copy: Blind copy: CN equals Tilo Netzer, OU equals EMD/O equals Merck) Blind copy. From: Lothar Finke/EMD Merck. Date 3rd of February 1997, 12:34:22. Topic: Litigation Scripts.

"Dear Professor Schnurr, on Friday of last week I was presented with a letter from the Legal Department in which I was requested to present a development plan for EMD 85189 by February 7th.

Since important data from Toxicology and Pharmacology are lacking, the EPG core team had projected September, October 1997. I consider it absolutely impossible to comply with this time frame from the Legal Department.

It is absolutely clear to me that it would help the process considerably if we had these documents. Nonetheless, I would like to warn against reacting too quickly, especially since these documents would then be used as subject matter in a litigation.

Before such documents leave our company, they must be thoroughly researched and worked through. It is unacceptable to submit a draft which would at most have the

value of a declaration of intent but which would be used -- can we go back a bit -- which internally would at most have the value of a declaration of intent but which externally could be used as argumentation -- would be used as argumentation before a court of law. This would cause us to have a lack of credibility.

I hope that you agree with my opinion and inform me accordingly. Sincerely yours, L. Finke."

BY MR. FLORES:

Q. In the second paragraph of the letter where you refer to the use of these documents as subject matter in a litigation, what litigation were you referring to?

[5] What litigation were you referring to?

A. This is February 1997, so I was certainly referring to this litigation.

Q. And what was the basis for your understanding that these documents, quote, "will then be used as subject matter in a litigation"?

A. Well, I assumed in the situation, being confronted with a litigation, that all documents produced for the clinical development of the substance would fall into other people's hands, and it's for this reason that I did not want to produce a draft outside of the time limits I had mentioned.

Q. Was it your understanding at the time you wrote this letter that the schedule that had been requested by the legal department would be used to support a claim that the present

research was being conducted for purposes of FDA review or the present experiments were being conducted for purposes of FDA review?

A. I cannot recall how I understood something that had been addressed to me from the legal department.

Q. Were you the only addressee on the letter from the legal department?

A. My problem is that I don't remember this, and that's why I do not recall who else could have been an addressee of this letter.

Q. You say you don't remember "this." what is the "this" that you're referring to?

A. The potential letter that has just been referred to.

Q. Why do you say "potential letter"?

A. Because I can't remember it.

Q. However, you did in fact come up with a development plan for EMD 85189 by February as requested by the Legal Department, didn't you?

* * * *

[D. Ex. at 1, 4, 5]

APPENDIX 56 — EXCERPT FROM DEPOSITION TESTIMONY OF SIMON L. GOODMAN, PH.D., DIRECTOR OF THE LABORATORY OF CELL ADHESION IN PRECLINICAL ONCOLOGY AT MERCK, GIVEN JULY 28, 1997, PLAYED AT TRIAL ON FEBRUARY 14, 2000

[Commencing at page 11]

integrin research and he was studying the biology of alpha-v series integrins.

Q. Did you have any understanding that one of Dr. Cheresh's roles as part of the collaboration between Merck and Scripps was to continue the screening process of potential alpha-v antagonists in a in vivo model?

A. Yes.

Q. What was that understanding based on?

A. Information which I received from my superiors and colleagues.

Q. Did you ever speak with Dr. Cheresh about the types of experiments he was performing for Merck?

A. Yes.

Q. Do you recall if that was also a basis for your conclusion that one of Dr. Cheresh's roles in the collaboration between Merck and Scripps was to continue the screening process of potential alpha v antagonists in an in vivo model?

A. I'm not sure if I'd call the role of Dr. Cheresh continuing the screening process.

I -- I mean we screened for activities and gave Dr. Cheresh active compounds which we wanted to find out if they were active in vivo, so I don't think Dr. Cheresh actually screened.

Q. Well, when you say you wanted to find out if they were active in vivo, wasn't that part of the purpose -- or the primary purpose of sending them to Dr. Cheresh, was to find out -- to screen out those that were not active in vivo?

A. Yes. But the compounds are -- because the compound is active in vitro doesn't mean to say it's going to be active in vivo. So maybe it's nit-picking to call that not screening, but I don't think it is actually screening its biological -- once again biological function.

Q. Your lab screened using in vitro model to find biologically active compounds, right? Wasn't one of the main purposes of Dr. Cheresh's lab to take those compounds and screen them yet again to find out which had biological activity in in vivo model?

A. I would describe it as a function of Dr. Cheresh's laboratory.

BY MR. BECKWITH:

Q. One of the functions of Dr. Cheresh's laboratory was to further screen those compounds using an in vivo model?

A. I've noted my problems with the word "screen," but accepting your definition of the word screen, yes.

Q. At some point in time did you learn that Dr. Cheresh was also doing comparative assays in the in vivo model between RGD containing cyclic peptides and nonpeptide compounds?

MR. CEPURITIS: You may answer yes or no, if you know.

A. Yes.

[12] BY MR. BECKWITH:

Q. When did you first learn that?

A. I can't give an exact date. I don't know an exact date, sometime during the course of this year, early this year.

Q. Sometime during the course of 1997?

A. I believe so, yeah.

Q. Do you have any understanding as to what the purpose is of those assays?

A. Yes.

Q. What do you understand the purpose to be?

MR. CEPURITIS: Only in general terms, please. This is not relevant, and I lodge an objection on that basis, but you may answer in general terms.

A. It's a search for biologically active compounds.

Q. When you say it's a search for biologically active compounds, does that include searching through the nonpeptide compounds for biological activity?

MR. CEPURITIS: Objection. I believe it's asked and answered. Again, you may answer yes or no.

A. Yes.

* * * *

[D. Ex. at 11, 12]

APPENDIX 57 — EXCERPT FROM DEPOSITION TESTIMONY OF ULRIKE GRIMM, PH.D., EMPLOYEE OF MERCK AND PROJECT MANAGER FOR EMD-12 PROJECT, GIVEN MAY 11, 1999, PLAYED AT TRIAL ON FEBRUARY 14, 2000

[Commencing at page 13]

Q. Can the witness please state her full name for the record.

A. Ulrike Grimm.

Q. Did you receive a degree in 1988?

A. Yes.

Q. And what was your degree?

A. It was in pharmacy. In other words, in German it's called Apotheke.

Q. And when did you go back to school in Frankfurt?

A. 1991.

Q. And what did you study?

A. I graduated in pharmacology.

Q. And when did you receive your diploma in pharmacology?

A. 1994.

What degree did you receive? What type of degree did you receive in pharmacology?

A. A doctor degree.

Q. When did you begin to work for Merck KGaA?

A. In November 1997.

[14] Q. And what were your duties and responsibilities when you first began to work for Merck KGaA?

A. I started working as a project manager.

Q. And what project were managing?

A. I was in charge of the project ED 121974?

Q. Is that EMD 121974?

A. Yes. EMD.

Q. To your knowledge, Dr. Grimm, has the FDA played any role in the design of any experiments carried out by Merck regarding EMD 121974?

A. Directly, no. But through guidelines, probably.

BY MR. BECKWITH:

Q. When you say "through guidelines probably" --

MR. CEPURITIS: objection. objection to the translation. (A German word) I don't think is probably. That's most -- (a German word) I don't think is "probably." It's most certainly or certainly so.

THE INTERPRETER: Do you want to --

MR. CEPURITIS: Let me look it up. I have a little dictionary here.

THE INTERPRETER: Do you want to rephrase it?

MR. BECKWITH: Do you want to see if the witness can rephrase it?

MR. CEPURITIS: (A German word), according to the Oxford German dictionary, means "certainly." If she says (a German word), that would mean most probably. So take your pick. She said (a German word).

BY MR. BECKWITH:

Q. Let me ask another question.

What first-hand information do you have, Dr. Grimm, concerning the role the FDA played if any in the design of any experiments carried out by Merck?

MR. CEPURITIS: objection, asked and answered.

A. I can only repeat what I said before. We observed the guidelines but we had no direct contact with the FDA.

BY MR. BECKWITH:

Q. What guidelines are you referring to?

A. I cannot give you a detailed answer because each team leader is responsible for his particular area

* * *

[18] Q. Is it true that as of February 26th, 1998, a decision had not yet been made on the pursuit of clinical trials phase IIa and IIb?

A. This decision was made on the 26th of February.

Q. So prior to February 26th, 1998, Merck had not yet decided whether to pursue clinical trials phase IIa and IIb in the United States for EMD 121974, correct?

A. Yes.

Q. Dr. Grimm, if you could turn to page M 02845.

A. Yes.

Why does it say EMD 85189, rather than EMD 121974?

A. Because at first the hydrochloride was developed and examined, and then later on it was changed over to (the interpreter spoke with the witness in German) -- it was changed to inner salt 121974.

Q. Were any side reaction pharmacology tests carried out with EMD 121974 or only EMD 85189?

A. The specific examinations for the side effects of 85189 were conducted, and the side effects of 121974 were stated in the toxicological reports.

BY MR. BECKWITH:

Q. Was any of the side effect pharmacology testing performed at the Scripps Research Institute?

A. As far as I'm informed, they were not.

Q. Turning to M02846, were any of the pharmacokinetic metabolism tests performed at the Scripps Research Institute?

A. As far as I'm informed, they were not.

Q. Turning to M 02847, were any of the toxicology studies performed at the Scripps Research Institute?

A. No.

* * *

[20] Q. Turning to page M 02858, did you prepare this page?

A. Yes, I have prepared this page after information by a team member from the marketing department.

Q. What does "NPV" stand for?

A. Net Present Value.

Q. What does "peak sales" mean?

A. Those are the sales after the fifth year of marketing.

Q. And there is some handwriting on the document. Do you know whose handwriting that is?

A. No.

Q. Do you know, for example, why it says first and third?

A. That assumably means first on the market and third on the market.

Q. So, for example, under the indication of breast cancer, you were assuming if you were first to the market you would have peak sales after five years of 332 million deutsche marks?

A. Yes.

Q. If you were third to the market, you would have 111 million deutsche marks in peak sales after five years?

A. Yes.

Q. And the net present value would be 4 million Deutsche marks if you were first to the market?

A. Yes.

Q. And it you were third to the market, the net present value would be a negative 280 million deutsche marks?

A. I can only assume that, because these figures are not mine. I do not know that.

Q. Turning to page M 02859, did you prepare [21] this page?

A. Yes, also according to information of a team member from marketing.

Q. Did you believe it to be accurate at the time you prepared it?

A. Yes.

Q. Do you recall having any discussions with anyone concerning the importance of being first into the market?

A. Only in general. The figures indicate how important it is to be number one on the market.

Q. And you believe that it was important to be first to the market in order to receive the maximum amount of profit?

A. Yes.

Q. What input if any have you received from the FDA in the course of carrying out your work in preparing the IND application?

A. We have to this point not received any information from the FDA, as far as I recall.

* * * *

[D. Ex. at 13, 14, 15, 17, 18, 19, 20, 21]

APPENDIX 58 — EXCERPT FROM DEPOSITION TESTIMONY OF ALFRED JONCZYK, PH.D., HEAD OF LABORATORY OF BIOLOGICAL CHEMISTRY AT MERCK, GIVEN JULY 30, 1997, PLAYED AT TRIAL ON FEBRUARY 23, 2000

[Commencing at page 33]

Q. Dr. Jonczyk, would you turn to your declaration which we've marked as Exhibit No. 42.

A. I'm doing so.

Does the 15189 compound contain unnatural amino acids?

A. Because in the EMD 85819 we have an N-methylated amino acid, I term this one an unnatural amino acid, whereas in contrast in the D-form we have only coded natural amino acids.

MR. CEPURITIS: Excuse me. I believe you misspoke. It's EMD 85189.

THE INTERPRETER: I'm sorry. That's what I meant to say.

Q. When you refer to 66203 as containing only natural amino acids, what did you mean by the term "natural"?

A. Natural amino acids are coded amino acids. Natural amino acids are coded amino acids. And my testimony was wider than that, in that I said that the EMD 66203 contains one of those natural coded amino acids, which occurs in the D-form.

Q. When you said natural amino acids are coded amino acids, what did you mean by the term "coded"?

A. By coded amino acids we mean those amino acids which are coded by the triplets of DNA.

Q. Does the D-form of amino acids occur in nature?

A. I cannot answer this.

Q. Is that because you don't know the answer?

A. I do not know the answer.

* * *

[35] Q. I assume, am I correct, that Merck provided Dr. Cheresh with that compound 66203 for the specific purpose of determining -- of having Dr. Cheresh determine whether it was a selective inhibitor of the vitronectin receptor; is that correct?

A. This assumption is correct.

Q. Why did Merck send it to Dr. Cheresh for that reason? Why Dr. Cheresh?

A. We sent the substance to Dr. Cheresh because with a laboratory of Dr. Cheresh we had enlarged our capacity with the aim of finding vitronectin receptor antagonists.

Q. Did Merck have the capacity of -- did Merck have the ability to determine whether 66203 was a selective inhibitor of the vitronectin receptor?

A. No. At that time we did not have the capacity of determining this on our own.

Q. And what was it that Merck lacked that deprived it of that capacity?

A. What we were lacking were the respective binding tests.

Q. Could you be more precise in identifying those tests, please?

A. Dr. Cheresh's alpha-v-beta-3 binding tests and cell adhesion tests of different kinds had been established.

Q. Have those tests now been established at Merck?

A. At Merck now some of these tests have been established as well.

Q. Was Dr. Cheresh's role at Scripps in connection with the discovery we've just been talking about that's described in the first sentence of paragraph 3 of your declaration -- was his role -- did his role consist of running the appropriate tests on the compounds provided to him by Merck?

Let me qualify that. The antagonist compounds or potential antagonist compounds.

* * *

[37] A. I refer to the two active peptides EMD 66203 and EMD 85189.

Q. At the time in 1995 when Merck began to formulate the plan referred to in the first sentence of paragraph 5 of your declaration, had either -- had 66203 been determined to have a significant inhibitory effect on angiogenesis?

A. I am not quite sure, but I think that at this time the effect of 66203 on angiogenesis was known.

Q. What was known about it at that time?

A. Again, I must say that I'm not sure, but I think that -- I'm not sure about this point, but the role of alpha-v-beta-3 in angiogenesis was I think known, and I -- and as I believe the inhibitory effect in vivo of the substance was known.

Q. Was that known through experiments performed by Dr. Cheresh?

A. If it was known, it was known through the experiments by Dr. Cheresh.

Q. When was an evaluation working group first established to consider 66203 if such a group was ever established as a suitable drug development candidate?

A. A formal evaluation group for the substance EMD, 66203 was never established.

Q. Was a formal group -- when was a -- when if at all was a formal working group to evaluate EMD 85189 as a suitable candidate for drug development first established?

A. As I expressed on page 3, an evaluation group for the substance EMD 85189 was installed in order to present the results of the evaluation to the directors of preclinical research in October 1996.

Q. Going back to exhibit A to your declaration, specifically -- strike that. I should ask you this. This letter shows you as having received a copy an the second page?

[38] A. This is correct.

Q. Do you recall receiving a copy of this letter on or about the date that's indicated as the date of the letter?

A. Yes. I'm very certain I received a copy

Q. And did -- Is the letter -- Insofar as it describes the meeting that you had with Dr. Linden, Mr. LaGuardia and Mr. Bingham in New York, is it accurate?

A. This letter describes the meeting accurately.

Q. Have all toxicology studies being carried out -- been carried out by Merck?

A. So far there is no GLP study which has been carried out.

Q. What is a GLP study?

A. A GLP toxicological study and GLP stands for Good Laboratory Practice.

Q. Okay. So no GLP toxicology study has been carried out?

A. Yes.

Q. Is one planned?

A. Yes.

Q. Is there a schedule for that to occur?

A. It should start up now in the near future.

Q. And near future being a matter of weeks or months?

A. It means weeks.

Q. And who is to carry out that study?

A. Our department for toxicology is in charge of toxicological studies at Merck.

Q. The same paragraph we've been talking about contains the phrase "Once we have defined a product for the pipeline."

Do you see that?

[39] A. Yes, I see that phrase.

Q. Had a product for the pipeline been defined at the time of the letter?

A. A product for the pipeline had not been designated at that time.

Q. What was the role of the -- of Dr. Friedlander and those people in his laboratory in the cooperative relationship with Scripps that is the subject of the letter that's Exhibit A to your declaration?

A. The role of Dr. Friedlander was to make certain models for testing in angiogenesis available.

Q. What is Dr. Nicolaou's role in connection with the present cooperation between Merck and the Scripps Research Institute?

A. Dr. -- In the cooperation Dr. Nicolaou offers us additional synthesis capacity.

Q. Synthesis for what?

A. Synthesis of chemical compounds.

Q. Does Dr. Nicolaou participate in the design of the compounds that are to be synthesized?

A. Yes, he participates in the design.

Q. Are the compounds that he designs all organic compounds?

A. All the compounds which he designs are organic compounds.

Q. And are any of them -- have any of the compounds he has designed been peptides?

A. None of the compounds he designed was a peptide.

Q. Who does Dr. Nicolaou -- or who, if anyone, does Dr. Nicolaou work with at Merck in the design of compounds?

A. Dr. Nicolaou designs his compounds on his own.

* * *

[42] A. Even today we do not know whether all these tests are suitable and will be accepted by FDA.

Q. Have compounds other than cyclopeptides been sent to Scripps for evaluation pursuant to the Research Funding and Option Agreement that became effective July 1, 1995?

A. Yes.

Q. How many?

A. (*IN ENGLISH*): I don't know exactly, but maybe ten, but I don't know.

Q. And have these compounds, whatever their number, been tested by Dr. Cheresh for effects, for anti-angiogenesis effects?

A. These compounds have been tested by Dr. Cheresh with regard to anti-angiogenic effects.

Q. The work done by Scripps pursuant to the cooperative agreement with Merck, comparing RGD peptides and nonpeptide inhibitors, could you tell me the purpose of that work?

A. I have not said that a comparison between RGD peptides and nonpeptidic inhibitors is actually being carried out by Scripps.

What I wanted to express and what I expressed is that I do not know whether any such comparison is being made at Scripps.

Q. Is it necessary to make such a comparison in order to carry out the preclinical work required for the development project on the EMD 121974 and 85189 compounds?

A. No, it is not necessary to make such a comparison.

Q. Would you clarify for me, please, the decision of the Pharmaceutical Project Steering Committee in November of 1996 to formally approve the developmental project? You on page 24 -- I'm sorry. On paragraph 8, line 24 of your declaration you say "The committee formally voted to develop this compound." That's 85189, correct?

* * * *

[D. Ex. at 33, 35, 37, 38, 39, 42]

APPENDIX 59 — EXCERPT FROM DEPOSITION TESTIMONY OF ALFRED JONCZYK, PH.D., HEAD OF LABORATORY OF BIOLOGICAL CHEMISTRY AT MERCK, GIVEN JULY 30, 1997, PLAYED AT TRIAL ON FEBRUARY 23, 2000

[Commencing at page 49]

Q. Dr. Jonczyk, with respect to the CAM model studies that are performed by Dr. Cheresh, they are performed -- I use the term chicken eggs. I think that's probably not correct. What is the right correct scientific term?

A. This CAM model is performed on chicken embryos.

Q. Embryos. Okay. Are studies -- are these CAM studies suitable for drawing inferences with respect to human toxicity effects?

A. I cannot imagine that a legislator would permit the toxicity or nontoxicity on chicken to be used. It is my understanding -- and I'm not an expert -- that toxicology studies must be performed on different animals.

Q. Different than chicken embryos?

A. Different animals, different from chicken embryos.

Q. Same question with respect to the cell adhesion studies performed by Dr. Cheresh. Is it possible to draw inferences with respect to human toxicity from the activity of cells in those cell adhesion assays?

A. Again, the same thing for cell adhesion studies as we have said for the CAM chicken embryo studies. The data on

toxicology or nontoxicology obtained from such studies do permit inferences to be made, but I cannot imagine that a legislator would permit such data alone to be used as toxicology data, but I'm not an expert.

Q. For regulatory purposes, is 121974 the same or a different compound from 85189?

A. To my knowledge, these two substances are different from each other as regards regulatory aspects.

* * * *

[D. Ex. 49]

APPENDIX 60 — EXCERPT FROM DEPOSITION TESTIMONY OF GERD-ALBRECHT LUCKENBACH, PH.D., HEAD OF DEPARTMENT OF IMMUNOPHARMA-COLOGY AT MERCK, GIVEN ON JULY 25, 1997, PLAYED AT TRIAL ON FEBRUARY 15, 2000

[Commencing at page 55]

from Merck's Patent Department about Telios?

MR. CEPURITIS: Again, I caution the witness to answer only yes or no.

A. No.

BY MR. FLORES:

Q. Do you know if the Patent Department at Merck has been involved in evaluation of Telios-owned patents?

A. No.

Q. At the second meeting where the conclusion was reached to exchange the peptides, was there any discussion of licensing issues?

A. Let me say not Dr. Piershbacher, but Dr. -- or Mr. Towarnicki. I think he was -- he was not talking about licensing. He was talking about he would like to, sort of, that we, if ever.

Q. He would like to what?

A. Have agreement.

Q. An agreement about what?

A. I suppose licensing. You asked for licensing, whether they were --

Q. Yeah. So he indicated he would like to see a licensing agreement signed?

A. He would like to see.

Q. Was there a discussion about Telios' patent rights?

A. Not that I remember.

Q. Are you involved in the program for the EMD 121974 compound, cyclic peptide?

A. Am I involved in that program?

Q. Yes.

A. Well, look, I'm head of department.

Q. So the answer is "yes"?

A. The answer is yes.

Q. (THROUGH THE INTERPRETER): The cyclic peptide compounds that are presently in the development stage at Merck, those affect specific diseases that are targeted to specific diseases, correct?

A. Okay. (IN ENGLISH): Yes.

Q. The research agreement, however, is not limited to any specific disease but covers any disease --

A. Right.

Q. -- so in that respect the research agreement is broader than the development project for cyclic peptides, correct?

A. Yes. But I would point out again that for one particular disease other models for the development of a drug for a particular disease -- other models are supportive.

Q. Are supportive?

[62] Q. At the time this agreement was entered into, it had not been decided to narrow the research effort funding -- funded under this agreement to any specific compounds, had it?

A. No.

Q. And that decision still hasn't been made, has it?

A. To date?

Q. Yes. Let me make my question clear. I'm asking about the scope of this Research and Funding Agreement.

A. Yes.

Q. At the present time this Research and Funding Agreement is not limited to any specific compounds.

A. Yes.

Q. Is that correct?

A. Well, I think the activities have a bit changed.

Q. Have a bit changed?

A. Yes. We kept the sort of research scope, but we focussed on the clinical development of the two compounds. The numbers you know much better than I do.

Q. I still have to look them up.

A. Right. So do I.

Q. But despite that change in focus, is this agreement at the present time limited to those compounds and those compounds only?

A. No.

Q. These -- both of these compounds, 85189 and 12197, are for cancer indications, right?

A. Right.

Q. And for opthalmic?

A. Opthalmology, yes.

Q. Any other indications?

A. There are plenty of indications listed here, aren't there?

Q. No, but I'm talking about those two specific compounds. Are they being developed for any other indication?

A. Look again. When you say cancer and opthalmology, this is wide fields. You couldn't say just cancer and opthalmology. These are particular indications in these fields.

Q. But you would agree, wouldn't you, that the FDA is not going to be satisfied with toxicity data based on chicken embryos?

A. We are not working for the FDA. We are working -- we are developing a drug, and you need data which are not meant for the FDA which help us in the development. The FDA will afterwards get the data it requires.

BY MR. FLORES:

Q. At a later stage?

* * * *

[D. Ex. 55, 62]

APPENDIX 61 — EXCERPT FROM DEPOSITION TESTIMONY OF GABRIELE NOLL, PH.D., TEAM HEAD FOR EMD-8 TEAM AT MERCK, GIVEN JULY 24, 1997, PLAYED AT TRIAL ON FEBRUARY 22, 2000

[Commencing at page 65]

Q. Please give me a brief background sketch of your education starting with university.

A. I started studying biology in 1974. My title is Diplome Biologin. Then I did my doctorate. And after I completed my doctorate, I began to work in the pharmaceutical industry, and I've been with Merck since the first of July 1996.

Q. You use the term "preclinical phase." When does the preclinical phase start?

A. It begins when the steering committee has designated the project a development project.

Q. I must have misunderstood one of your earlier answers. I had asked you earlier what your duties and responsibilities in projects were prior to the project being designated a development project.

A. Yes.

Q. You identified one of those as tests required in the preclinical phase.

A. It's in the evaluation phase, in other words before the decision is taken by the steering committee as to whether

or not, yes or no, a project should be designated a development project. We have to prepare data to present to the steering committee for this purpose.

During this period of time the project manager is not yet responsible for the project.

Q. And the steering committee you were referring to earlier was the PPSC?

A. Yes.

[66] Q. Earlier you testified that you were manager responsible for the cyclopeptide project; is that correct?

A. I am head of this project.

Q. What is the cyclopeptide project?

A. It's also a development project in the field of anti-angiogenesis.

Q. And what compounds are being considered in connection with this project?

A. I don't know. For these types of questions, we have our specialists.

Q. As project manager, is it part of your duties and responsibilities to understand what compounds you may be managing?

A. No, that's not my responsibility.

Q. When you speak to people that you are responsible for managing, do they ever describe to you the compounds that they are working with?

A. To a certain extent, yes, but I really don't take note of such things, because I'm not a scientist in this capacity. I'm a project manager.

Q. When did you become the project manager for the cyclopeptide project?

A. On the 15th of November, 1996.

Q. What happened on the 15th of November 1996 that led you to becoming the manager of the cyclopeptide team?

A. I was given this responsibility from PPSC.

Q Was November 15, 1996, the date that PPSC designated the cyclopeptide project a development project?

A. That is the date when it officially became a development project.

Q. What kind of project was it prior to that date?

[67] A. The transition between research and development are often flowing transitions, and in the pre-phase it may have been a development project but not officially.

Q. Do you know whether it was a development project prior to November 15, 1996?

A. It was certainly a candidate for an official development project.

Q. How do you know that?

A. Otherwise the evaluation wouldn't have been carried out.

Q. So at some point aren't all compounds that Merck is working on a candidate for a development project?

A. No. In -- there are a number of phases of evaluation in research and development, and in some cases the decision is taken beforehand that it should not be a development project.

Q. When you use the term "candidate for an official development project," is that a generic term, or is that a term that has a specific meaning within Merck?

A. That's my private vocabulary.

Q. When did you first learn that Merck was exploring cyclopeptides?

A. I can't tell you precisely, but it must have been August or September.

Q. 1996?

A. 1996.

Who else was on the evaluation team?

A. I don't think I can remember all the names.

Q. Tell me as many as you can remember.

A. Okay. Dr. Jonczyk, Dr. Finke, Dr. Rohmann, [68] Dr. Uhl, U-H-L.

Q. And yourself?

A. Yes. And myself.

Q. What was Dr. Jonczyk's role on the evaluation team?

A. Dr. Jonczyk was and is the person who had a leading part from the side of Research and Development in the development of cyclic peptides.

Q. What was his role on the evaluation team?

A. Well at that time he was still the person responsible for this project.

Q. What was Dr. Rohmann's role on the evaluation team?

A. Dr. Rohmann is coming from Strategic Marketing.

Q. What was his role on the evaluation team?

A. Well, in an evaluation team we try to cover all the various disciplines, the preclinical, the clinical and the marketing one. It is normal in any development when we try to take a research project to product which is mature for the market. So we try to get everybody together at one table at an early stage.

Q. Was Dr. Rohmann responsible solely for marketing?

A. This is the part he plays, yes.

Q. What was Dr. Finke's role?

A. Dr. Finke is the representative of the clinical side.

Q. What was Dr. Uhl's role?

A. Dr. Uhl is also a project manager, just as I am.

Q. After the meeting of the PPSC, November 15, 1996, was a new group formed to pursue the development of cyclopeptide?

[69] A. Yes.

Q. What was the new group called?

A. EPG.

Q. What does EPG stand for?

A. Development Project Group. And we have a core team which is part of the EPG.

Q. What's the other part of the EPG?

A. Other specialized departments.

Q. What other specialized departments were part of the EPG for cyclopeptide?

A. They were and they are -- I'll try to be complete. I cannot guarantee completeness. There were specialists from Toxicology, Pharmacology, Pharmacokinetics, Clinical, Clinical Development, the Registration Department, Marketing, Production. I hope I have said all of them.

Q. Who are the members of the core group?

A. For preclinical development on the core team, it's Dr. Jonczyk, Dr. Finke and Dr. Netzer for the clinical part. For the marketing part, Dr. Rohmann, and I am the head.

Q. I'm going to mark as next in order minutes from the first core team meeting, EMD 85189.

A. These are the minutes of the first core team meeting.

Q. Was the first core team meeting on November 26, 1996?

A. I assume so, since it says that here.

Q. You don't have any reason to believe that that date is inaccurate?

A. No.

[71] Q. Okay. Now, when you came up with the rough time plan were -- was the time plan at all dependent upon when you got the information from toxicology and pharmacokinetics?

A. We consider what tests are ongoing and what reports are completed, and this is included in our time plan.

Q. And there were some tests that hadn't even begun yet, correct?

A. That's correct.

Q. And, therefore, your time plan -- your rough time plan that was presented to the PPOC -- PPSC was at least in part dependent upon those experiments taking place within a given period of time, correct?

A. Yes. As generally is the case, you have to take all of the activities that need to be carried out preclinically and clinically and to present them in a plan and how they fit together. And I as project manager have the responsibility of trying to have this as quickly as possible.

Q. What did you mean by the statement in the parentheses "models relevant to clinical trials"?

A. Right. In pharmacological experiments in research, they don't always -- they are not always of direct relevance to the clinical studies. They are more for scientific support. That is not the responsibility for this development project.

In my responsibility all I'm interested in is having the tests completed which are relevant from a clinical point of view.

Q. Just so I understand your answer, then, are there pharmacological experiments that are relevant to research that are not always directly relevant to clinical studies?

A. Yes. That's possible. In a company which [illegible]earch, there may be pharmacological experiments that we may not realize that they are important. They may only be of indirect importance. You have to make a clear distinction here between research and development.

Prior to January 21, 1997, was there a development plan for the toxicologic and pharmacokinetic analysis of EMD 85189?

[72] A. Not as I would consider a preclinical plan. For me a preclinical plan would consist of a written document several pages in length, similar to a clinical plan.

Q. On page 2 of Exhibit 11, under two-week tox study it states, "All pharmacological experiments have been performed on the mouse so far." Do you know who performed those experiments?

A. You mean the mouse experiments in pharmacology?

Q. Well, whatever the experiments were that you were referring to on page 2 of Exhibit 11 where you said "all pharmacological experiments have been performed on the mouse so far."

A. No, I cannot tell you exactly who that was. This was a comment from Dr. Jonczyk, who said that all of the pharmacological experiments have been performed.

Q. Have been performed on mouse?

A. On the mouse, relevant for toxicological studies.

THE INTERPRETER: For these toxicological studies.

A. Let me explain this. Perhaps we were thinking about whether these toxicological studies should be carried out in mice or in rats.

Q. And at this point in time the studies were planned or were in the planning stage. They hadn't yet begun?

A. Which studies?

Q. The toxicological studies you were just referring to.

A. Toxicological studies, the two weeks toxicological studies had not yet begun.

Q. What toxicological studies had taken place?

* * * *

[D. Ex. 65-69, 71-72]

APPENDIX 62 — EXCERPT FROM DEPOSITION TESTIMONY OF CLAUDE J. SCHMITGES, DIRECTOR OF PRECLINICAL PHARMA. RESEARCH AT MERCK, GIVEN JULY 24, 1997, PLAYED AT TRIAL ON FEBRUARY 14, 2000

[Commencing at page 76]

A. Claude Jochen Schmitges, J-O-C-H-E-N.

Q. And your current position with Merck?

A. My current position is Director of Biomedical Research.

Q. The -- Your curriculum vita states that in the time period 1994-'97 you were department head Cardiovascular Biology Preclinical Pharma Research of E. Merck.

A. That's correct.

Q. Now, beginning in 1997, you became the Director of Biomedical Research, Preclinical Pharma Research.

A. Yes, that's correct.

Q. Preclinical Pharma Research -- strike that. That was the same division as your earlier --

A. That's the same division, but before I was responsible just for the Cardiovascular Department, and now I am overseeing the cardiovascular, the CNS, and the Oncology Department.

Q. How many people do you supervise in your current position?

A. Between 270 and 280 people.

Q. When was the first time that you, yourself, came into any kind of contact with anyone from Telios?

A. I can't recall exactly. Several years before I visited the La Jolla Cancer Research Foundation and had a discussion with Erkki Ruoslahti just about general scientific matters; and at that time he introduced me to Michael Piershbacher, but we didn't talk about any project. It was just a scientific discussion. That was my first contact with Dr. Michael Piershbacher. But we never talked about licensing -- licensing compounds or anything like that at that time.

Q. That -- you said several years before. Was that several years before the summer of 1994?

A. Yeah. It was -- I don't recall the year exactly, but it must have been around 1990.

Q. And how is it that you came to visit the La Jolla Cancer Research Foundation?

A. I had few days between two meetings in California and visited several scientific groups in the La Jolla area.

Q. Why did you choose to visit Dr. Ruoslahti?

A. Because he is an expert in the integrin field, and in 1990 we started to consider to start a [77] program on Glycoprotein IIb IIIa inhibitors, GP Roman IIB Roman IIIa, small A, inhibitors.

Q. In your discussion with Dr. Ruoslahti, did you inform him of the potential that Merck might launch a development program for this particular integrin antagonist?

A. It was not a development program. We discussed whether we should start a research program on Glycoprotein IIb IIIa inhibitors.

Q. Perhaps you should explain for the record the difference between the research program and a development program.

A. Research program means that we try to identify compounds that have activity in this field, whereas development means the testing of such compounds in animals to do toxicology studies and to test them in human-beings.

Q. Development projects are focussed on regulatory requirements; is that correct?

A. Yes. This is primarily toxicology and testing in human -- in trials in humans.

Q. And research programs are not oriented to regulatory requirements?

A. Not at all, no. They are much more proximal. It's a start of a project.

Q. Were patents mentioned?

A. Not to my recollection.

Q. Prior to the meeting with Telios, again July 15, 1994, had you had any discussions with people from Merck about what could and could not be disclosed about Merck's own activities?

A. No, I don't recall any such discussions. If I may mention, you can see it from the program, that there was just

one item. It was a presentation of the Telios activities so there was -- it was not on the program presentation of Merck activities.

Q. Was there any kind of agreement reached at that meeting about further contacts?

A. We expressed -- Merck expressed its interest in the TP-9201. The profile presented by Michael Piershbacher sounded very attractive, and it seemed to complement our own profile, our own compounds; and as far as I recall, there was interest of Merck in the PepTite program, but I was not involved in that.

I was only involved in the TP-9201 activities, and definitely there was interest, and we asked for material to be sent to Merck. Sorry, I should say "material" means information, just details about the profile, study protocols. I mean written information.

* * *

[79] A. It was not planned to have these comparative trials to be done at Merck. It was planned to have them done at the lab of Lucchesi in Ann Arbor, Michigan. That was a lab in which -- which has great experience in the testing of such class -- this class of compounds.

Q. What kind of tests were to be conducted?

A. These were tests in a dog model of myocardial infarction.

Q. Were those tests conducted?

A. These tests were conducted.

Q. Were the protocols for the tests looked at by you and your people from your department?

A. We looked at the test protocol and the people from Telios looked at the test protocol.

Q. In your opinion were the test protocols satisfactory?

A. It seemed satisfactory to us, yes.

Q. And what were the results of the tests?

A. The tests were quite disappointing. I mean it's a very complicated story, and eventually the tests were conducted in three phases because Telios was not happy at all with the result of the first and second phase. And so there were long negotiations with Lucchesi, the lab that conducted these trials; and eventually three different experiments were done to really give TP-9201 a chance to show its superiority.

Q. What was your overall assessment of the results of those tests?

A. The results were very, very disappointing. We didn't see significant advantage. We didn't see a significant superiority of TP-9201 over MK 9 -- 6 -- sorry -- 383.

Q. And did you communicate that conclusion to Telios?

A. Definitely. We -- during the course of these experiments there were many contacts between Merck and Telios and Lucchesi. I myself met with Michael Piershbacher at Lucchesi's lab in Ann Arbor to make sure that really the optimum was obtained from these experiments to make sure that everything was okay with the tests; and when even the third phase didn't show the superiority of TP-9201, we had this meeting which is mentioned here in the deposition in I

think May 1996 in which we together looked at the data, the data from the three phases of the Lucchesi experiments; and there was no difference in opinion that these results didn't show the superiority of TP-9201, which Telios and we ourselves had expected from these trials or these experiments.

* * * *

[D. Ex. 76, 77, 79]